PB89-119531

Health and Environmental Effects Profile for 2-Methoxyethanol

(U.S.) Environmental Protection Agency
Cincinnati, OH

Nov 86

U.S. Department of Commerce
National Technical Information Service
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TECHNICAL REPORT DATA

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1. REPORT NO. EPA/600/X-87/025	2.	3. RECIPIENT'S ACCESSION NO. PB89 119531/AS
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for 2-Methoxyethanol		5. REPORT DATE November 1986
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

The Health and Environmental Effects Profile for 2-Methoxyethanol was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. 2-Methoxyethanol has been determined to be a systemic toxicant. A Reference Dose (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for 2-methoxyethanol is 0.001 mg/kg/day for inhalation exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 2-methoxyethanol is 100.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS *(This Report)* Unclassified	21. NO. OF PAGES 129
	20. SECURITY CLASS *(This page)* Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB89-119531

EPA/600/X-87/025
November 1986

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR 2-METHOXYETHANOL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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CINCINNATI, OH 45268

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U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA. 22161

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

2-Methoxyethanol (CAS number 109-86-4), also known as ethylene glycol monomethyl ether, is a colorless, almost odorless, viscous liquid. Glycol ethers, such as 2-methoxyethanol, undergoes most of the reactions that are typical of alcohols (Dow Chemical Co., 1981; Hawley, 1981). 2-Methoxyethanol is reportedly produced on a commercial scale by a total of six manufacturers. During 1983, 83.026 million pounds of 2-methoxyethanol were produced in the United States and 9.465 million pounds were exported (SRI, 1985; USITC, 1984; U.S. Department of Commerce, 1984). 2-Methoxyethanol is usually produced on a commercial scale by reacting ethylene oxide with anhydrous methanol. Excluding exports, the following use pattern for 2-methoxyethanol has been reported: jet fuel additive (56%); solvent for protective coatings (11%), other solvent uses (23%); synthesis of di(2-methoxyethyl) phthalate (3%) and synthesis of 2-methoxyethanol acetate and other esters (7%) (U.S. EPA, 1982; Lawler, 1977). Consumer products that could potentially contain 2-methoxyethanol include perfumes, nail polishes, wood stains, enamels, varnishes and lacquers (U.S. EPA, 1982).

If released to water, 2-methoxyethanol is not likely to undergo hydrolysis or oxidation. 2-Methoxyethanol is reported to be susceptible to biodegradation in acclimated and unacclimated waters seeded with activated sludge (Mills and Stack, 1954; Thom and Agg, 1975; Dow Chemical Co., 1981). A pure culture study using G. suboxyans indicated that α-methoxyacetic acid was the resulting product of 2-methoxyethanol biooxidation (Deley and Kersters, 1964). Vapor-liquid equilibrium data (Dow Chemical Co., 1981) suggest that volatilization should be significant and rapid from all surface waters. Adsorption to suspended solids and sediments and bioaccumulation in

aquatic organisms should not be significant. If released to air, the hydroxyl reaction half-life of vapor phase 2-methoxyethanol is estimated to be 17.54 hours (U.S. EPA, 1986b). Reaction with ozone is not likely to be significant (U.S. EPA, 1986b). Physical removal of 2-methoxyethanol from the atmosphere by wet deposition may be significant because of the complete water miscibility of the compound. If released to soil, 2-methoxyethanol is not likely to hydrolyze. Pure culture studies indicate 2-methoxyethanol is capable of supporting some isolated soil microbes, but not others. Isolated Alcaligenes MC11 oxidized 2-methoxyethanol to methoxyacetic acid. 2-Methoxyethanol should be highly mobile in soils. Volatilization from both dry and wet soils should be significant (Dow Chemical Co., 1981). The importance of the biodegradation of 2-methoxyethanol in soils in comparison with its evaporative and leaching losses cannot be evaluated with the available data.

2-Methoxyethanol has tentatively been identified in advanced waste treatment water from Pomona, CA, and drinking water from New Orleans, LA (Lucas, 1984). Potential sources of release to the aquatic environment are in the effluent from production and use facilities, and from consumer products at waste disposal sites. Atmospheric release may result from emissions from production and use facilities, and minor emissions may result from consumer products. Approximately 103,500 workers in a wide variety of occupations are projected to be exposed to 2-methoxyethanol (RTECS, 1985). Adsorption through the skin is the recognized route of entry by 2-methoxyethanol into the body of workers exposed to this compound (Clapp et al., 1984). The general population may be exposed by dermal contact with consumer goods that contain 2-methoxyethanol (U.S. EPA, 1982); however, no monitoring data indicating the exposure to this compound by the general population in air, water or food were found in the available literature.

The available data indicate that 2-methoxyethanol is relatively nontoxic to fish and crustaceans in acute exposures. No LC_{50} values <10,000 mg/ℓ were reported for six species of fish and two crustaceans. Flagellate protozoans appeared to be more sensitive, with toxicity thresholds of 2.2 and 1715 mg/ℓ reported for C. paramecium and E. subcatum, respectively (Bringmann and Kuehn, 1981). Of the algae and bacteria tested, the blue-green alga, M. aeruginosa, with a toxicity threshold of 100 mg/ℓ, was more sensitive than the green alga, S. quadricauda, or the bacterium, P. putida, both with toxicity thresholds >10,000 mg/ℓ (Bringmann and Kuehn, 1978, 1980).

2-Methoxyethanol is readily absorbed across isolated human abdominal epidermis in vitro (Dugard et al., 1984). Rats dosed orally absorbed ~90% of a radioactive dose (Miller et al., 1983a). Absorption following oral, inhalation and cutaneous exposure can be inferred from toxicity studies using animals and from human exposure data. Selective accumulation of 2-methoxyethanol has not been observed in several target tissues (e.g., testes, thymus and spleen). 2-Methoxyethanol-derived radioactivity does accumulate somewhat in embryonic tissues relative to maternal plasma (Scott and Nau, 1985), especially in those tissues with high metabolic rates (Sleet et al., 1985a). The majority of 2-methoxyethanol-associated radioactivity (up to 70%) is excreted in the urine with lesser amounts contained in expired air (primarily as CO_2) and feces (Moss et al., 1985; Miller et al., 1983a; Foster et al., 1984). Up to 95% of the radioactivity in the urine is in the form of methoxyacetic acid, the predominant metabolite of 2-methoxyethanol (Miller et al., 1983, 1984; Moss et al., 1985). Studies comparing the relative toxicities of methoxyacetic and 2-methoxyethanol and the inhibitory effects of alcohol dehydrogenase inhibitors on 2-methoxyethanol toxicity strongly suggest that 2-methoxyethanol is primarily oxidized to methoxyacetic acid by its corresponding aldehyde followed by excretion in the urine or by conjugation with glycine to form methoxyacetylglycine, which is also excreted in the urine (Ritter et al., 1985; Foster et al., 1983; Sleet et al., 1985b).

Pertinent data regarding the carcinogenicity of 2-methoxyethanol could not be located in the available literature as cited in the Appendix.

Results from several mutagenicity assays suggest that 2-methoxyethanol is not a significant genotoxic agent. Reverse mutation (Ong, 1980; McGregor et al., 1983; McGregor, 1984), DNA repair (McGregor et al., 1983), chromosome aberration (McGregor et al., 1983), sex-linked recessive lethal (McGregor et al., 1983) and point mutation (McGregor, 1984) assays were negative. Dominant lethal and sperm abnormality assays yielded some positive results (McGregor et al., 1983; Chapin et al., 1985a), although effects were observed only at high doses and it is not clear whether genetic mechanisms were involved in the response.

Acute and subchronic studies have revealed that 2-methoxyethanol mainly exerts effects on the blood, kidneys, liver, testes, spleen, central nervous system and developing fetus. Chronic studies using 2-methoxyethanol could not be located in the available literature as cited in the Appendix.

Oral and inhalation exposure to 2-methoxyethanol has resulted in fetotoxic and embryolethal effects in several species. Oral administration of 2-methoxyethanol to JCL-ICR mice at doses ranging from 31.25-1000 mg/kg/day on gestation days 7-14 resulted in fetal mortality at doses $\geq$250 mg/kg/day and decreased fetal weights at 125 and 250 mg/kg. The incidence of skeletal malformations was significantly higher in the 62.5, 125 and 250 mg/kg groups.

Skeletal variations and retarded fetal ossification were evident in all treatment groups. Maternal effects included decreased weight gain in the ≥250 mg/kg groups and a decreased leukocyte count in the high-dose group. Thus, even at the lowest dose, 31.25 mg/kg, significant embryotoxic effects were observed (Nagano et al., 1981).

Phase-specific teratogenicity was elicited in CD-1 mice receiving 100-500 mg/kg 2-methoxyethanol orally during various periods between days 7 and 14 of gestation (Horton et al., 1985). Administration of 250 mg/kg/day during gestation days 7-14 resulted in gross malformations similar to those reported by Nagano et al. (1981). Exencephaly was the predominant lesion resulting from administration during the early stages of gestation (gestation days 7-9); whereas paw malformations were prevalent during later stages of development, becoming maximal on gestation day 11. Evaluation of the dose-response relationship for digit anomalies following a single dose on gestation day 11 revealed a NOEL of 100 mg/kg while malformations resulted at 175 mg/kg. At higher doses, malformations with concomitant decreases in fetal weight were observed.

The incidence of malformed fetuses (hydronephrosis, heart defects and short limbs and tails) was significantly increased in Wistar rats receiving 159 or 319 mg/kg 2-methoxyethanol on gestation day 12. Equimolar doses of methoxyacetic acid, a metabolite of 2-methoxyethanol, were similarly potent, indicating that it may be the proximate teratogen (Ritter et al., 1985). Treatment of time-mated Sprague-Dawley rats with 25, 50 or 100 mg 2-methoxyethanol/kg/day on gestation days 7-13 resulted in a 100% resorption rate in the high-dose group and an increased incidence of gross cardiovascular malformation in the 50 mg/kg group. There was a dose-related increase in

EKG abnormalities at ≥25 mg/kg, with a prolonged QRS wave being the most prevalent aberration in both the 25 and 50 mg/kg groups (Toraason et al., 1985a).

A preliminary study in monkeys indicated that oral doses of 2-methoxyethanol as low as 97 mg/kg given during short periods of pregnancy resulted either in abortions or malformed offspring (Scott, 1984).

Teratogenic responses have also been induced following inhalation exposure. Treatment of pregnant Sprague-Dawley rats on gestation days 7-13 or 14-20 or male rats for 6 weeks with 78 mg/m^3 2-methoxyethanol, 7 hours/day resulted in significant neurochemical deviations in the brains of 21-day offspring from both maternally- and paternally-exposed groups (Nelson et al., 1984a). Alterations were most prevalent in the brainstem and cerebrum and less numerous in the cerebellum and midbrain. A significant decrease in avoidance conditioning in offspring from dams exposed on days 7-13 was the only evidence of altered behavior. No effects on maternal or paternal animals were observed (Nelson et al., 1984a). In a related study, vapor concentrations of 2-methoxyethanol, which were not maternally toxic, produced complete resorptions at 622 mg/m^3 and increased resorptions, reduced fetal weights and skeletal and cardiovascular anomalies at both 311 and 156 mg/m^3 when administered 7 hours/day on gestation 7-15 (Nelson et al., 1984b). Neither study established a no-effect level for embryotoxicity.

Hanley et al. (1984) compared the teratogenic potency of 2-methoxyethanol in CF-1 mice, F-344 rats and New Zealand White rabbits by exposing dams, 6 hours/day to 9 (rats and rabbits), 31 or 156 mg/m^3 on gestation days 6-15 (rats and mice or 6-18 rabbits). Offspring from rats and mice exposed to 156 mg/m^3 showed no evidence of a teratogenic effect, although indications of slight fetotoxicity (minor skeletal variations) were observed in both species. Exposure in the high-dose rabbit group produced significant increases in the incidence of malformations, minor variations and resorptions as well as decreases in mean fetal body weight. Transient decreases in maternal body weight gain in all high-dose groups were the only consistent signs of maternal toxicity. No significant treatment-related effects on fetal development were observed in any species exposed to ≤31 mg/m^3 for 6 hours/day.

Reproductive performance and testicular function can be substantially compromised by oral or inhalation 2-methoxyethanol exposure. Rats treated orally with 2-methoxyethanol on gestation days 9-15 caused 100% resorptions at a 100 mg/kg/day dose level, while 50 mg/kg/day significantly depressed litter size and fetal body weights (Toraason et al., 1985b). Total resorption was also observed in CD-1 mice following oral administration of 1400 mg/kg/day 2-methoxyethanol on days 7-14 of gestation (Smith, 1983). The lowest dose of 2-methoxyethanol (estimated by the authors to be 779 mg/kg/day for males) in a 15-week drinking water study by Gulati et al. (1985) resulted in a 1 and 6% fertility index for female and male CD-1 mice, respectively. These authors additionally observed marked testicular degeneration and decreased spermatogenesis in male mice treated similarly for 19 weeks.

Reduced testicular weight and tubular degeneration were evident in F344 rats treated orally with 500 mg/kg/day 2-methoxyethanol for 4 days. No testicular changes were observed in animals given 100 mg/kg/day (Grant et al., 1985). Testicular degenerations were also reported in JCL-ICR mice given ≥250 mg/kg/day 2-methoxyethanol by gavage, 5 times/week for 5 weeks. Animals given doses of ≤125 mg/kg/day exhibited no adverse effects (Nagano et al., 1979). These investigators, using the same protocol, produced testicular degeneration in Syrian golden hamsters given 62.5-500 mg/kg/day and in guinea pigs given 250 or 500 mg/kg/day (Nagano et al., 1984).

Oral ingestion of 2-methoxyethanol by Sprague-Dawley rats at dosages of 50, 100, 250 or 500 mg/kg/day for up to 11 days resulted in testicular damage characterized by primary spermatocyte lesions in all but the low-dose treatment group (Foster et al., 1983). Treatment with 500 mg/kg/day for 4 days produced widespread degeneration and decreased testis weight, effects that were reversible after 8 weeks (a period equivalent to one full maturation cycle). Similarly, F344 rats dosed orally with 100 or 200 mg/kg/day 2-methoxyethanol for 5 consecutive days exhibited time- and dose-related decreases in sperm concentration and motility as well as marked testicular degeneration. In addition, changes in testicular protein and enzyme levels were observed in these treatment groups (Chapin et al., 1985b). In both of these studies, a dose of 50 mg/kg/day did not produce significant alterations in testicular morphology or function.

Fertility was completely suppressed in male Sprague-Dawley rats exposed to 934 mg/m^3 2-methoxyethanol, 6 hours/day, 5 days/week for 13 weeks, but was partially restored at 13 weeks postexposure (Rao et al., 1983). Decreased testicular size and atrophic tubules were also observed in these animals. Female rats exposed to the same concentration did not exhibit any adverse reproductive effects (Rao et al., 1983). No effects on fertility and reproduction were observed at 311 mg/m^3 in rats. Doe et al. (1983), however, reported adverse reproductive effects in Wistar rats exposed to 311 mg/m^3, 6 hours/day during gestation days 6-17. Litter production and the number, weight and viability of the pups were reduced at this dose. Exposure to 934 mg/m^3 resulted in the delivery of no litters. Male rats exposed to this same dose for 10 days experienced reduced testicular weight and tubular atrophy while a dose of 311 mg/m^3 had no effect in males.

A number of effects were observed in Sprague-Dawley rats and New Zealand White rabbits exposed to 93, 311 or 934 mg/m³ 2-methoxyethanol vapor, 6 hours/day, 5 days/week for 13 weeks (Miller et al., 1983b). The high dose resulted in reduced body, thymus and testicular weights as well as hematological alterations and testicular degeneration in both species. Mortality was also increased in rabbits in the 311 and 934 mg/m³ treatment groups. Testicular alterations were observed in the mid- and low-dose rabbit groups, while rats at these doses displayed no apparent effects (Miller et al., 1983b). No testicular effects were found in rabbits similarly exposed to 0, 3, 10 or 30 ppm (0, 9, 31 or 93 mg/m³) for 13 weeks (Miller et al., 1982).

Following a single 4-hour exposure to 2-methoxyethanol vapor, a dose-related decrease in testis weight was observed in Alpk/AP rats exposed to 3890, 7780 or 15,560 mg/m³ 2-methoxyethanol. Minimal degenerative changes were seen in the testis of rats exposed to concentrations ≥1945 mg/m³ (Samuels et al., 1984).

A similar pattern of effects was reported by Miller et al. (1981) following exposure of F344 rats and B6C3F1 mice to 311, 934 or 3112 mg/m³ 2-methoxyethanol, 6 hours/day for a total of 9 days during an 11-day period. The high-dose groups displayed significant adverse effects on body weight gain, peripheral blood counts, bone marrow, testes and lymphoid tissues. Similar but less severe effects were observed at the 934 mg/m³ dose level.

Impaired reproductive capacity was the result of subcutaneous injection of 39 or 242 mg/kg/day 2-methoxyethanol on days 6-20 of gestation in Wistar rats. No litters were produced in the high-dose group, while the low-dose animals produced fewer litters than controls (Doe, 1984).

Administration of 250 mg/kg 2-methoxyethanol by intraperitoneal injection resulted in a depleted spermatocyte population in Sprague-Dawley rats 24 hours after dosing (Moss et al., 1985).

Nonreproductive effects of 2-methoxyethanol exposure generally involve alterations in hematology, the thymus and in the central nervous system. An altered hematological profile was elicited in Wistar rats exposed to 965 mg/m^3 2-methoxyethanol, 7 hours/day, 5 days/week for 5 weeks and dogs similarly exposed to 2334 mg/m^3 for 12 weeks (Werner, 1943a,b). Male F344 rats that were given 2-methoxyethanol per os for 4 consecutive days at doses of 100 or 500 mg/kg/day exhibited dose-dependent changes in the hematological profile that were generally reversible within 3 weeks after the cessation of treatment (Grant et al., 1985). Reversible reductions in relative kidney, spleen and thymus weights were also observed. Nagano et al. (1979) reported a sharp decrease in the white cell count of JCL-ICR mice given oral doses of 2-methoxyethanol $\geq$500 mg/kg/day, 5 times/week for 5 weeks. Similarly, Doe et al. (1983) reported significant reductions in a number of blood indices as well as depressed body weight gain and reduced thymus size in Wistar rats exposed to 934 mg/m^3 2-methoxyethanol, 6 hours/day for 10 consecutive days. Rats in a 311 mg/m^3 dose group were hematologically similar to controls.

Foster et al. (1983) reported that male Sprague-Dawley rats treated orally with $\geq$100 mg/kg/day for 7-11 days experienced reductions in relative liver weight while animals given 50 mg/kg/day were unaffected. House et al. (1985) administered 2-methoxyethanol by gavage to B6C3F1 mice at dosages of 250, 500 or 1000 mg/kg/day, 5 days/week for 2 weeks and noted a sharp reduction in thymus weights in the mid- and high-dose groups. Alterations in biochemical parameters in isolated glial cells from Wistar rats were observed following exposure to $\geq$156 mg/m^3 2-methoxyethanol, 6 hours/day for up to 2 weeks (Savolainen, 1980). Increased mortality was reported by

Smith (1983) in CD-1 mice after oral administration of 1520 or 3045 mg/kg/day for 8 consecutive days. This effect was also observed following the consumption of drinking water containing 5.0% 2-methoxyethanol by CD-1 mice for 2 weeks (Gulati et al., 1985). At a drinking water concentration of 2.5%, mice suffered significant weight losses while mice maintained on water containing $\leq$1.0% displayed no overt effects of toxicity.

Human exposure episodes have resulted in only one reported fatality following ingestion (Young and Woolner, 1946). Occupational exposure to 2-methoxyethanol vapors has generally resulted in transient hematologic, neurologic and renal deficits. Moderate cases of anemia and toxic encephalopathy are the symptoms most often reported to be the results of inhalation, oral or dermal exposure to 2-methoxyethanol in the workplace (Donley, 1936; Parsons and Parsons, 1938; Greenburg et al., 1938; Zavon, 1963; Nitter-Hauge, 1970; Ohi and Wegman, 1978; Cohen, 1984). Occupational exposures to concentrations of $\leq$20 ppm ($\leq$62 mg/m^3) appear to result in no overt effects.

The acute toxic effects of 2-methoxyethanol generally are similar to those induced by longer term exposures with the brain, kidneys and blood being the primary target organs. Generally, 2-methoxyethanol is relatively low in acute oral toxicity, mildly irritating to the eyes, not appreciably irritating to the skin, may be absorbed through the skin but is not significantly toxic by this route and is somewhat more toxic when inhaled (Rowe and Wolf, 1982). Oral LD_{50} values range from 0.89 g/kg in rabbits to 3.4 mg/kg in female rats (Carpenter et al., 1956) while dermal LD_{50}s in rabbits range from 1.3-2.0 g/kg (Carpenter et al., 1956; Dow, n.d.). A wide range of acute inhalation exposure situations (from 1556-17,601 mg/m^3) has resulted in increased mortality and renal and hematological disturbances (Goldberg et al., 1962; Carpenter et al., 1949, 1956; Werner et al., 1943c).

An RfD of 0.001 mg/kg/day or 0.1 mg/day for a 70 kg man is proposed based on the rabbit NOEL of 31 mg/m^3 obtained from the Miller et al. (1982) subchronic inhalation study. A CS of 26.6 and an RQ of 100 were derived from a chronic human MED of 14 mg/day based on neurochemical alterations in offspring from male rats exposed to 25 ppm (78 mg/m^3), 7 hours/day for 6 weeks (Nelson et al., 1984a). Because no carcinogenicity data were located, 2-methoxyethanol was classified as an EPA Group D chemical.

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LIST OF ABBREVIATIONS

BODT	Biological oxygen demand list
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EKG	Electrocardiogram
K_{ow}	Octanol/water partition coefficient
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

2-Methoxyethanol is also known by the synonyms ethylene glycol monomethyl ether, glycolmethyl ether, methyl glycol and 2-hydroxyethyl methyl ether. Trade names for 2-methoxyethanol include Dowanol EM, Methyl Cellosolve, Methyl Oxitol and Poly-Solv EM (U.S. EPA, 1986a). The structure, molecular weight, empirical formula and CAS number are as follows:

$$CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-}OH$$

Molecular weight: 76.09

Empirical formula: $C_3H_8O_2$

CAS Registry number: 109-86-4

1.2. PHYSICAL AND CHEMICAL PROPERTIES

2-Methoxyethanol is a colorless, almost odorless, viscous liquid (Hawley, 1981). Its odor has been characterized as being pleasant and sweet (Verschueren, 1983). 2-Methoxyethanol is miscible in water and nonaqueous solvents such as alcohol, ether, glycerol, acetone, dimethylformamide (Windholz, 1983), ketones and glycols (Hawley, 1981). Selected physical properties are as follows:

Freezing point	-121°F (-85°C)	Dow Chemical Co., 1981
Boiling point:	124.6°C	Dow Chemical Co., 1981
Vapor pressure:		
at 20°C	6.2 mm Hg	Verschueren, 1983
at 25°C	9.5 mm Hg	Dow Chemical Co., 1981
at 30°C	14 mm Hg	Verschueren, 1983
Water solubility:	completely miscible	Dow Chemical Co., 1981
Log octanol/water partition coefficient:	-0.77	Hansch and Leo, 1985
Specific gravity (25/25°C):	0.963	Dow Chemical Co., 1981

Vapor density (air=1):	2.62	Verschueren, 1983
Flashpoint:		
open cup	43.3°C	U.S. EPA, 1982
closed cup	39.4°C	U.S. EPA, 1982
Threshold limit value (air):	25 ppm (skin)	Sax, 1984
Conversion factor (air at 20°C):	1 mg/m^3=0.32 ppm 1 ppm=3.1 mg/m^3	Verschueren, 1983

Glycol ethers, such as 2-methoxyethanol, undergo most of the reactions that are typical of alcohols (Dow Chemical Co., 1981). 2-Methoxyethanol presents a moderate fire risk when exposed to heat, and it can react with oxidizing materials to form explosive peroxides (Sax, 1984).

1.3. PRODUCTION DATA

2-Methoxyethanol is currently manufactured on a commercial scale by the following companies (SRI, 1985):

Eastman Kodak (Texas Eastman)	Longview, TX
ICI Americas	Bayport, TX
Olin Corp.	Bradenburg, KY
Union Carbide	Taft, LA

USITC (1985) also listed PPG Industries and Texaco as manufacturers of 2-methoxyethanol in 1984. Domestic production of 2-methoxyethanol during 1982 and 1983 has been reported to be 89.323 and 83.026 million pounds, respectively (USITC, 1983, 1984). During 1983, 9.465 million pounds of 2-methoxyethanol were exported (U.S. Dept. of Commerce, 1984). 2-Methoxyethanol is usually produced commercially by reacting ethylene oxide with anhydrous methanol (U.S. EPA, 1982). This reaction results in a mixture of monomethyl ethers of diethylene, triethylene and the higher glycols from which 2-methoxyethanol must be separated (U.S. EPA, 1982). Temperature, pressure, reactant molar ratios and catalysts are selected to give the desired product mix. 2-Methoxyethanol may also be produced by the reaction of ethylene glycol with diazomethane or by the reaction of ethylene chlorohydrin or ethylene glycol with sodium hydroxide and dimethyl sulfate (U.S. EPA, 1982).

1.4. USE DATA

Excluding exports (12.5%), the following use pattern for 2-methoxyethanol has been reported (Lawler, 1977):

jet fuel additive	56%
solvent for protective coatings	11%
other solvent uses	23%
synthesis of di(2-methoxyethyl) phthalate	3%
other intermediate uses	7%

A number of potential consumer products contain 2-methoxyethanol. These products include perfumes, in which this compound is used as a fixative, nail polishes, wood stains, enamels, varnishes and lacquers (U.S. EPA, 1982).

1.5. SUMMARY

2-Methoxyethanol (CAS number 109-86-4), also known as ethylene glycol monomethyl ether, is a colorless, almost odorless, viscous liquid. Glycol ethers, such as 2-methoxyethanol, undergoes most of the reactions that are typical of alcohols (Dow Chemical Co., 1981; Hawley, 1981). 2-Methoxyethanol is reportedly produced on a commercial scale by a total of six manufacturers. During 1983, 83.026 million pounds of 2-methoxyethanol were produced in the United States and 9.465 million pounds were exported (SRI, 1985; USITC, 1984; U.S. Department of Commerce, 1984). 2-Methoxyethanol is usually produced on a commercial scale by reacting ethylene oxide with anhydrous methanol. Excluding exports, the following use pattern for 2-methoxyethanol has been reported: jet fuel additive (56%); solvent for protective coatings (11%), other solvent uses (23%); synthesis of di(2-methoxyethyl) phthalate (3%) and synthesis of 2-methoxyethanol acetate and other esters (7%) (U.S. EPA, 1982; Lawler, 1977). Consumer products that could potentially contain 2-methoxyethanol include perfumes, nail polishes, wood stains, enamels, varnishes and lacquers (U.S. EPA, 1982).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. WATER

2.1.1. **Hydrolysis.** Glycols, ethers and alcohols are generally resistant to hydrolysis (Lyman et al., 1982). Experimental hydrolysis data regarding 2-methoxyethanol were not located; however, hydrolysis of 2-methoxyethanol in the aquatic environment is not expected to be important.

2.1.2. **Oxidation.** The rate constant for the reaction between 2-methoxyethanol and hydroxyl in water at pH 9.0 and room temperature has been reported to be 8.1×10^{8} M^{-1} sec^{-1} (Anbar and Neta, 1967) and 1.56×10^{9} M^{-1} sec^{-1} (Dorfman and Adams, 1973). Assuming an ambient HO radical concentration of 10^{-17} M in water (Mill et al., 1980), the reaction half-life has been estimated to be >1 year. Therefore, this reaction should have no significant environmental importance.

Pertinent data regarding aquatic reaction between 2-methoxyethanol and singlet oxygen or RO_2 radical could not be located in the available literature as cited in the Appendix.

2.1.3. **Photolysis.** Pertinent data regarding the photolysis of 2-methoxyethanol in the aquatic environment could not be located in the available literature as cited in the Appendix.

2.1.4. **Microbial Degradation.** The Dow Chemical Co. (1981) reported 5-, 10- and 20-day BODTs for 2-methoxyethanol of 39, 77 and 77%, respectively. A 20-day BODT of >50% indicates the product will be largely removed in a biological waste treatment plant; a 20-day BODT of 10-50% indicates it will be partially removed (Dow Chemical Co., 1981). Using a settled domestic wastewater as seed, Price et al. (1974) measured 5-, 10- and 20-day BODTs of 30, 62, 74 and 88%, respectively, in unacclimated freshwater and 6, 18, 23 and 39%, respectively, in unacclimated seawater. Heukelekian and Rand

(1955) reported 5-day BODT values ranging from 4-16% and 10-day BODT values ranging from 22-26%. Mills and Stack (1954) measured 65% BODT after 10 days incubation with activated sludge. Thom and Agg (1975) reported that 2-methoxyethanol should be degraded by biological sewage treatment provided suitable acclimation is achieved. Deley and Kersters (1964) isolated the acetic acid bacteria, G. suboxyans, and determined the resulting product of 2-methoxyethanol biooxidation is α-methoxyacetic acid. Pure culture studies with the fungus, Aspergillus versicolor and P. aeruginosa revealed that 2-methoxyethanol actively inhibited the growth of these microorganisms (Stahl and Pessen, 1953). Biodegradation studies with microorganisms isolated from industrial oil-water emulsions revealed that 2-methoxyethanol was quite susceptible to oxidation by P. 324 and P. oleovorans, but showed no degradation by P. formicans or F. brevis (Ellis et al., 1956). Although no experimental data were found, it appears that biodegradation of the compound in natural water will be a significant fate process.

2.1.5. Transport.

2.1.5.1. VOLATILIZATION -- The vapor-liquid equilibrium of water and 2-methoxyethanol at 760 mm Hg has been determined by the Dow Chemical Co. (1981). When the percent by weight of 2-methoxyethanol in the liquid phase is <5%, the percent by weight of 2-methoxyethanol in the vapor phase is approximately equal to the percentage in the liquid phase. Therefore, the air-to-water ratio is ~1.0, which is the value of the unitless Henry's Law Constant. Conversion to units yield a Henry's Law Constant of 2.4×10^{-2} atm m^3/mol. This value of Henry's Law Constant indicates that volatilization should be both significant and rapid from all surface waters (Lyman et al., 1982). Even though 2-methoxyethanol is completely miscible in water, the vapor-liquid equilibrium data suggest that volatilization of 2-methoxyethanol from water should be environmentally significant.

2.1.5.2. ADSORPTION -- Experimental data regarding the adsorption of 2-methoxyethanol to suspended solids and sediments in water could not be located in the available literature as cited in the Appendix. Considering the complete water solubility of this compound and its estimated K_{oc} of 9-60 (Section 2.3.3.), physical adsorption to suspended solids and sediments should not be significant.

2.1.5.3. BIOACCUMULATION -- Experimental data regarding bioaccumulation of 2-methoxyethanol in aquatic organisms could not be located in the available literature as cited in the Appendix. A BCF of 0.15 was calculated, based on a log K_{ow} value of -0.77 (see Section 1.2.) and using the following equation (Lyman et al., 1982): $\log BCF = 0.76 \log K_{ow} - 0.23$. The complete water solubility of 2-methoxyethanol also predicts that bioaccumulation of 2-methoxyethanol in aquatic organisms should be insignificant.

2.2. AIR

2.2.1. Reaction with HO Radical. The rate constant for the reaction between vapor phase 2-methoxyethanol and photochemically generated HO radical has been estimated to be 1.372×10^{-11} cm^3/molecule-sec at 25°C (U.S. EPA, 1986b). Assuming an ambient HO radical concentration of 8.0×10^5 molecules/cm^3, the hydroxyl reaction half-life has been calculated to be 17.54 hours (U.S. EPA, 1986b). This value for the half-life indicates that significant removal from the atmosphere may take place by reaction with hydroxyl radicals.

2.2.2. Reaction with Ozone. 2-Methoxyethanol is not expected to react with ozone in the atmosphere (U.S. EPA, 1986b).

2.2.3. Photolysis. Pertinent data regarding the direct photolysis of 2-methoxyethanol in the troposphere could not be located in the available literature as cited in the Appendix.

2.2.4. Physical Removal Processes. Because of its complete water miscibility, significant amounts of 2-methoxyethanol may be removed from the atmosphere by wet deposition; however, any 2-methyoxyethanol removed by dissolution into clouds or washout is likely to revolatilize (see Sections 2.1.5.1. and 2.3.4.).

2.3. SOIL

2.3.1. Chemical Degradation. Based on the molecular structure of 2-methoxyethanol, this compound is not likely to hydrolyze (Lyman et al., 1982). Other pertinent data regarding the chemical degradation of 2-methoxyethanol in soil could not be located.

2.3.2. Microbial Degradation. Harada and Hagashima (1975) isolated the bacteria Alcaligenes MC11 from soil and found that this microorganism was capable of using 2-methoxyethanol as a sole source of carbon for aerobic growth. 2-Methoxyethanol underwent biooxidation by A. MC11 to methoxyacetic acid (Harada and Hagashima, 1975). 2-Methoxyethanol did not support the growth of the bacteria Alcaligenes TE8 and Corynebacterium OEH8 isolated from enriched soil samples (Harada and Nagashima, 1975). Fincher and Payne (1962) isolated a bacterium from a soil enriched with triethylene glycol and found that 2-methoxyethanol was not used as a sole source of carbon for the growth of this microorganism. Water and soil biodegradation studies indicate that biodegradation in soils may be important. The significance of biodegradation in comparison to other loss processes such as volatilization and leaching in soils cannot be evaluated with the available data.

2.3.3. Leaching. The complete WS and relatively low K_{ow} of 2-methoxyethanol suggest that it may be readily leached into the soil environment, although there are no experimental data available to confirm this prediction. The K_{oc} has been estimated using the molecular topology and quantitative structure-activity analysis of Sabljic (1984) and using the following equation (Lyman et al., 1982): $\log K_{oc} = 0.544 \log K_{ow} + 1.377$ and a log K_{ow} value of -0.77 (see Section 1.2.). Estimated K_{ow} values of 9 and 60, respectively, indicate that 2-methoxyethanol should be highly mobile in soil (Swann et al., 1983).

2.3.4. Volatilization. In a standard volatilization test conducted at 77°F (25°C) and 15% relative humidity, 2-methoxyethanol lost 100% weight by evaporation in 16 minutes (Dow Chemical Co., 1981). This suggests that 2-methoxyethanol will evaporate quite rapidly from dry soil surfaces. Evaporation from moist soils may also be significant since the compound evaporates rapidly from water.

2.4. SUMMARY

If released to water, 2-methoxyethanol is not likely to undergo hydrolysis or oxidation. 2-Methoxyethanol is reported to be susceptible to biodegradation in acclimated and unacclimated waters seeded with activated sludge (Mills and Stack, 1954; Thom and Agg, 1975; Dow Chemical Co., 1981). A pure culture study using G. suboxyans indicated that α-methoxyacetic acid was the resulting product of 2-methoxyethanol biooxidation (Deley and Kersters, 1964). Vapor-liquid equilibrium data (Dow Chemical Co., 1981) suggest that volatilization should be significant and rapid from all surface waters. Adsorption to suspended solids and sediments and bioaccumulation in aquatic organisms should not be significant. If released to air, the hydroxyl reaction half-life of vapor phase 2-methoxyethanol is estimated to be 17.54 hours (U.S. EPA, 1986b). Reaction with ozone is not likely to be significant (U.S. EPA, 1986b). Physical removal of 2-methoxyethanol from the atmosphere by wet deposition may be significant because of the complete water miscibility of the compound. If released to soil, 2-methoxyethanol is not likely to hydrolyze. Pure culture studies indicate 2-methoxyethanol is capable of supporting some isolated soil microbes, but not others. Isolated A. MC11 oxidized 2-methoxyethanol to methoxyacetic acid. 2-Methoxyethanol should be highly mobile in soils. Volatilization from both dry and wet soils should be significant (Dow Chemical Co., 1981). The importance of the biodegradation of 2-methoxyethanol in soils in comparison to its evaporative and leaching losses cannot be evaluated with the available data.

3. EXPOSURE

3.1. WATER

2-Methoxyethanol has been tentatively identified in advanced waste treatment water from Pomona, CA, and in drinking water from New Orleans, LA (Lucas, 1984). 2-Methoxyethanol may be released to the aquatic environment in the effluent from production and use facilities. Release at waste disposal sites from consumer products that contain 2-methoxyethanol could potentially cause contamination of surface and groundwaters.

3.2. FOOD

Pertinent monitoring data regarding the presence of 2-methoxyethanol in food could not be located in the available literature as cited in the Appendix.

3.3. INHALATION

Environmental release of 2-methoxyethanol to air may result from emissions from production and use facilities. It has been reported that 2-methoxyethanol content of the aqueous condensate stream during methanol-based glycol ether production is 0.94 g/kg; however, the ultimate disposition of this stream was not stated (U.S. EPA, 1982). Emission from consumer products such as paints and varnishes may be a minor source of release to the atmosphere (Clapp et al., 1984).

The National Occupational Hazard Survey prepared by NIOSH projects that 103,459 workers are occupationally exposed to 2-methoxyethanol (RTECS, 1985). Some occupations in which workers may be exposed to 2-methoxyethanol in the atmosphere are drum fillers (0.1-2.8 ppm), aircraft refuelers (<1.0-4.7 ppm) (Clapp et al., 1984), painters [108 mg/m^3 (34.2 ppm)] (Love and Donohue, 1983), cellophane sealers, dry cleaners, oil and wax processors, printers, stainers, textile dryers, and makers of cleaning solutions, film, hydraulic fluid, inks, lacquers, nail polish and plastics (U.S. EPA, 1982).

Pertinent monitoring data regarding 2-methoxyethanol in the ambient atmosphere could not be located in the available literature as cited in the Appendix.

3.4. DERMAL

The general population may be exposed to 2-methoxyethanol by dermal contact with consumer products that contain this compound, such as perfumes, nail polishes, wood stains, enamels, varnishes and lacquers (U.S. EPA, 1982). Adsorption of 2-methoxyethanol through the skin is the recognized route of entry into the body by workers exposed to this compound (Clapp et al., 1984).

3.5. SUMMARY

2-Methoxyethanol has tentatively been identified in advanced waste treatment water from Pomona, CA, and drinking water from New Orleans, LA (Lucas, 1984). Potential sources of release to the aquatic environment are in the effluent from production and use facilities, and from consumer products at waste disposal sites. Atmospheric release may result from emissions from production and use facilities, and minor emissions may result from consumer products. Approximately 103,500 workers in a wide variety of occupations are projected to be exposed to 2-methoxyethanol (RTECS, 1985). Adsorption through the skin is the recognized route of entry by 2-methoxyethanol into the body of workers exposed to this compound (Clapp et al., 1984). The general population may be exposed by dermal contact with consumer goods that contain 2-methoxyethanol (U.S. EPA, 1982); however, no monitoring data indicating the exposure to this compound by the general population by air, water or food are available in the literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

2-Methoxyethanol administered orally was rapidly and extensively absorbed through the gastrointestinal tract of rats, as up to ~90% of the radioactivity was recovered in the carcass, skin, urine and expired air during a 48-hour period following a single dose of 1-8.7 mmol/kg (76-662 mg/kg) ^{14}C-2-methoxyethanol (ethanol-labeled) in water (Miller et al., 1983a). Dugard et al. (1984) measured the absorption of several undiluted glycol ethers across isolated human abdominal epidermis *in vitro*. 2-Methoxyethanol was the most readily absorbed glycol ether tested and had a rate of absorption of 2.82 mg/cm^{3}/hour. The development of systemic signs of toxicity following inhalation and dermal exposure to 2-methoxyethanol strongly indicates that absorption occurs by these routes (Chapter 5).

4.2. DISTRIBUTION

Forty-eight hours after a single oral dose or 8.7 mmol/kg (662 mg/kg) of ^{14}C-2-methoxyethanol (ethanol-labeled) in water to male rats, the blood retained the highest amount of radioactivity/g of tissue of the ^{14}C remaining in the carcass (Miller et al., 1983a). Table 4-1 summarizes the tissue distribution of ^{14}C, and demonstrates that some of the primary target organs of 2-methoxyethanol toxicity (e.g., testes, thymus and spleen) do not accumulate 2-methoxyethanol-derived radioactivity since the ^{14}C concentration in these tissues is considerably lower compared with the blood. Dajani (1969) reported that 2-methoxyethanol is equally distributed in brain, plasma, lung and liver 1 hour following administration by an unspecified route in rats and mice, while fat contained ~10% less than other tissues. Although 2-methoxyethanol is a testicular toxin, no testis-specific uptake of 2-methoxyethanol-derived radioactivity was observed in

TABLE 4-1

Tissue Distribution of Radioactivity in Male Rats 48 Hours After a Single Oral Dose of 8.7 mmol/kg of ^{14}C-Methoxyethanol[a]

Tissue	Tissue/Blood[b]	Percentage of Dose[c]
Body	0.19	9.60±0.89
Liver	0.66	1.57±0.32
Kidney	0.35	0.20±0.00
Blood	1.00	0.67±0.21
Testes	0.19	0.13±0.06
Fat	0.05	NC
Thymus	0.03	0.02±0.00
Spleen	0.29	0.03±0.00
Total		12.17±0.43

[a] Source: Miller et al., 1983a

[b] Ratio of the mean ^{14}C in tissue to the mean ^{14}C in blood for three animals (units of tissue and blood concentration were not reported).

[c] Numbers are mean ± SD percentage of dose for three animals.

NC = Not calculated

rats, as only 0.15% of the dose was located in the testes 24 hours after a single oral dose of 500 mg/kg ^{14}C-2-methoxyethanol in water (Foster et al., 1984).

Because 2-methoxyethanol is a potent teratogen (Section 5.3.), distribution studies have been conducted in pregnant mice and rats. Sleet et al. (1985a) administered a single oral dose of ^{14}C-2-methoxyethanol to CD-1 mice on gestation day 11 and followed the distribution of radioactivity in maternal and fetal tissues. Five minutes after gavage, 2-methoxyethanol was generally distributed throughout most tissues, although the gastrointestinal tract lumen, adipose tissue and amniotic fluid contained lesser amounts of ^{14}C. By 30 minutes, radioactivity had cleared from maternal nervous and muscle tissue, while radioactivity remained in liver, blood, glands and periosteum. Radioactivity was also evident in the placenta and yolk sac as well as in embryonal limb buds, somites and neuroepithelium. The maternal liver retained the most ^{14}C 12 hours following gavage, while at 24 and 48 hours, radioactivity persisted in liver, bone marrow, placenta and embryos, although levels had declined from earlier time points. At 48 hours, paw and digit anlagen, bone marrow and neuroepithelium had persistent elevations in ^{14}C compared with other tissues. Thus, the conceptus is readily accessible to 2-methoxyethanol-derived radioactivity, which appears to preferentially locate in tissues with high metabolic rates (Sleet et al., 1985a).

Scott and Nau (1985) injected 400 mg/kg of 2-methoxyethanol in Wistar rats on day 12 of pregnancy and monitored the concentration of methoxyacetic acid, a major metabolite and the presumed proximate teratogen, in maternal plasma and embryo homogenate. Accumulation of the metabolite in the embryo was evidenced by embryonic to maternal plasma concentration ratios of 2.11, 2.19 and 2.09 when measured 2, 8 and 24 hours after administration, respectively.

4.3. METABOLISM

The profile of radioactivity in a sample of urine collected from male rats during a 0- to 12-hour time period following oral doses of 1 and 8.7 mmol/kg (76 and 662 mg/kg) ^{14}C-2-methoxyethanol (ethanol-labeled) revealed that 83 and 95%, respectively, of the urinary radioactivity was contained in a single peak that corresponded to methoxyacetic acid (Miller et al., 1983a). It appears, therefore, that 2-methoxyethanol was oxidized to methoxyacetic acid, presumably by an alcohol dehydrogenase. Approximately 50-60% of the dose of radioactivity was excreted in the urine and 10-20% was more extensively metabolized and eliminated in the expired air as $^{14}CO_2$ following oral dosing of rats with ^{14}C-2-methoxyethanol (ethanol-labeled) at 76 or 662 mg/kg (Miller et al., 1984).

Administration of 250 mg/kg ^{14}C-2-methoxyethanol (methoxy-labeled) intraperitoneally to male rats resulted in the recovery of 55% of the radioactivity in the urine within 48 hours, of which 50-60% and 18-25% were identified as methoxyacetic acid and methoxyacetylglycine, respectively. 2-Methoxyethanol was rapidly converted to methoxyacetic acid in the plasma ($t_{1/2}$ for disappearance of 2-methoxyethanol = 0.6 hours), while clearance of radioactivity from the plasma had a $t_{1/2}$ of 19.7 hours. Pretreatment with pyrazole, an alcohol dehydrogenase inhibitor, markedly reduced the amount of radioactivity in urine and the proportion of methoxyacetic acid in the urine, and increased the half-times for 2-methoxyethanol disappearance and radioactivity clearance from the plasma (Moss et al., 1985). Foster et al. (1984) reported that urinary radioactivity following a single oral dose of ^{14}C-2-methoxyethanol (methoxy-labeled) consisted predominantly of methoxyacetic acid (73.1%), 2-methoxyethanol (14.8%) and an unidentified metabolite (8.1%).

One form of human liver alcohol dehydrogenase was shown to use 2-methoxyethanol as a substrate with a K_m of 1×10^{-3} and a Vmax 40% that of ethanol (Blair and Vallee, 1966). This finding lends support to the proposed pathway of 2-methoxyethanol oxidation to its corresponding acid by formation of an acetaldehyde.

Additional evidence for the oxidation of 2-methoxyethanol can be found in studies comparing the relative toxicity of 2-methoxyethanol and methoxyacetic acid. Equimolar amounts of 2-methoxyethanol and methoxyacetic acid were equally potent on elicitng a teratogenic response in rats, and the administration of 4-methylpyrazole provided significant protection against 2-methoxyethanol (Ritter et al., 1985). Equivalent doses of 2-methoxyethanol and methoxyacetic acid produced similar degrees of testicular toxicity following oral administration to rats (Foster et al., 1983). In addition, Sleet et al. (1985b) reported that the embryotoxicity of 2-methoxyethanol is due to alcohol dehydrogenase catalyzed oxidation.

In summary, the available evidence indicates that 2-methoxyethanol is predominantly oxidized by an aldehyde to methoxyacetic acid, which is either excreted in the urine or further metabolized to the corresponding glycine conjugate.

4.4. EXCRETION

Three studies in which male rats were dosed orally or intraperitoneally with ^{14}C-2-methoxyethanol produced similar patterns of excretion with 55-70% of the radiolabel appearing in the urine after a 48-hour period (Moss et al., 1985; Miller et al., 1983a; Foster et al., 1984). Forty-eight hours following a single oral dose of ^{14}C-2-methoxyethanol (labeled in the ethanol carbons), 54.3, 2.7 and 12.2% of the administered radioactivity were recovered in the urine, feces and expired air, respectively, when a low dose

(76 mg/kg) was given; while 63.2, 2.6 and 12.1% of the ^{14}C, respectively, were recovered following a high (662 mmol/kg) dose (Miller et al., 1983a). A single oral dose of 500 mg/kg ^{14}C-2-methoxyethanol (methoxy-labeled) resulted in 70% of the dose appearing in the urine after 48 hours, while the feces and expired air contained 1.5 and 2.7% of the administered radioactivity, respectively (Foster et al., 1984). The difference between these two studies in the amount of radiolabel found in the expired air is probably due to a difference in the position of the label in the parent compound (ECETOC, 1985). An intraperitoneal dose of 250 mg/kg ^{14}C-2-methoxyethanol (methoxy-labeled) resulted in 55.2% of the dose being excreted in the urine within 48 hours; the bulk of the ^{14}C (>70%) was excreted during the first 24 hours (Moss et al., 1985).

4.5. SUMMARY

2-Methoxyethanol is readily absorbed across isolated human abdominal epidermis _in vitro_ (Dugard et al., 1984). Rats dosed orally absorbed ~90% of a radioactive dose (Miller et al., 1983a). Absorption following inhalation and cutaneous exposure can be inferred from toxicity studies in animals and from human exposure situations (Chapter 5). Selective accumulation of 2-methoxyethanol has not been observed in several target tissues (e.g., testes, thymus and spleen). 2-Methoxyethanol-derived radioactivity does accumulate somewhat in embryonic tissues relative to maternal plasma (Scott and Nau, 1985), especially in those tissues with high metabolic rates (Sleet et al., 1985a). The majority of 2-methoxyethanol-associated radioactivity (up to 70%) is excreted in the urine with lesser amounts contained in expired air (primarily as CO_2) and feces (Moss et al., 1985; Miller et al., 1983a; Foster et al., 1984). Up to 95% of the radioactivity in the urine is in the form of methoxyacetic acid, the predominant metabolite of

2-methoxyethanol (Miller et al., 1983a, 1984; Moss et al., 1985). Studies comparing the relative toxicities of methoxyacetic and 2-methoxyethanol and the inhibitory effects of alcohol dehydrogenase inhibitors on 2-methoxyethanol toxicity strongly suggest that 2-methoxyethanol is primarily oxidized to methoxyacetic acid by its corresponding aldehyde followed by excretion in the urine or by conjugation with glycine to form methoxyacetylglycine, which is also excreted in the urine (Ritter et al., 1985; Foster et al., 1983; Sleet et al., 1985b).

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of 2-methoxyethanol could not be located in the available literature as cited in the Appendix. This chemical has been selected for general toxicology testing by National Testing Program (NTP, 1986).

5.2. MUTAGENICITY

Mutation assays performed using 2-methoxyethanol are summarized in Table 5-1. There is no evidence of mutagenic activity in the Ames test using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 with or without an S-9 activation system (Ong, 1980; McGregor et al., 1983). This system is limited, however, in that microsomal mixed-function oxidase systems do not permit alcohol oxidation by dehydrogenase enzymes. Thus, experiments were conducted in which β-NAD$^+$ and alcohol dehydrogenase were added to the test systems (McGregor et al., 1983; McGregor, 1984). Results of these experiments were generally negative, although the data are inconclusive because of the cytotoxicity of the system.

Results from mammalian in vitro point mutation assays are not suggestive of significant genotoxic activity (McGregor et al., 1983; McGregor, 1984).

The overall frequency of abnormally shaped sperm was increased significantly in B6C3F1 mice from 5.2% in air control to 9.4% in animals exposed to 500 ppm (1556 mg/m^3) 2-methoxyethanol 7 hours/day for 5 days (McGregor et al., 1983). Most of this increase was due to the significantly enhanced number of sperm with banana-shaped or amorphous heads. No increase was observed at the 25 ppm (78 mg/m^3) level. Similar results were reported by Chapin et al. (1985a), who administered 50, 100 or 200 mg 2-methoxyethanol/kg/day to F344 rats per os for 5 consecutive days. The percentage of

TABLE 5-1

Mutagenicity Testing of 2-Methoxyethanol

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Reverse mutation	*Salmonella typhimurium* TA98 TA100 TA1535 TA1537	plate incorporation	up to 200 mg/plate	±S-9 from Aroclor-induced rats	= = = =	NC	Ong, 1980
Reverse mutation	*S. typhimurium* TA98 TA100 TA1535 TA1537 TA1538	plate incorporation	up to 33 mg/plate	±S-9 from male rats	= = = = = =	Procedure included a 30-minute preincubation period; β-NAD⁺ and yeast alcohol dehydrogenase were added to some plates	McGregor et al., 1983
Reverse mutation	*S. typhimurium* TA98, TA100 TA102	plate incorporation	up to 100 mg/plate	β-NAD⁺, alcohol dehydrogenase	-	The quantity of β-NAD⁺ use was slightly toxic	McGregor, 1984
DNA repair	human embryonic intestinal fibroblasts	cell culture	up to 10 mg/mℓ for 3 hours	none	-	NC	McGregor et al., 1983
Chromosome aberration	male and female CD rat bone cells	inhalation; 7 hours/day for either 1 or 5 hours	25 ppm 500 ppm	none	- -	NC	McGregor et al., 1983
Sex-linked recessive lethal	*Drosophila*	inhalation; 1 hour (25 ppm) or 15 minutes (500 ppm)	25 ppm 500 ppm	none	see comment	Results somewhat ambiguous and difficult to interpret	McGregor et al., 1983
Sperm abnormality	B6C3F1 mice	inhalation; 7 hours/day for 5 days	25 ppm 500 ppm	none none	- +	Banana-shaped head and amorphous head were primary abnormalities	McGregor et al., 1983
Sperm abnormality	F344 rats	orally for 5 days	50 mg/kg/day 100 mg/kg/day 200 mg/kg/day	none	- + +	No hook, amorphous head and pin head were primary abnormalities	Chapin et al., 1985a

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Dominant lethal	CD rats	inhalation; 7 hours/day for 5 days	25 ppm 500 ppm	none	- ±	Reduced fertility in high dose males and could preclude detection of dominant lethal effects	McGregor et al., 1983
Dominant lethal	Sprague-Dawley rats	inhalation; 6 hours/day, 5 days/week for 13 weeks	30 ppm 100 ppm 300 ppm	none	- - -	Reversible male sterility at 300 ppm; no effects after recovery	Rao et al., 1983
Dominant lethal	F344 rats	orally for 5 days	50 mg/kg/day 100 mg/kg/day 200 mg/kg/day	none	- - ±	Authors concluded that 2-methoxyethanol is a very weak dominant-lethal agent at the high dose	Chapin et al., 1985a
Mammalian point mutation, *in vitro*	L5178Y mouse lymphoma $tK^{+/-}$ cells	cell culture	up to 100 μg/mℓ	male rat liver S-9 mix	-	NC	McGregor, 1984

NC = No comment; NR = not reported

morphologically abnormal sperm was significantly greater in the middle- and high-dose groups and the following abnormalities were observed (in order of decreasing frequency): no hook, amorphous head and pin head. Six weeks following dosing, the malformation frequency reached a maximum of 80% in the high-dose group and 53% in the low-dose group.

2-Methoxyethanol produced a weak response only at the highest doses in dominant lethal assays, and it is likely that the observed effects were the result of testicular toxicity rather than genotoxicity. CD rats exposed by inhalation to 25 or 500 ppm (78 or 1556 mg/m^3) 2-methoxyethanol, 7 hours/day for 5 days were serially mated at weekly intervals for 10 weeks to untreated females (McGregor et al., 1983). Although pregnancy frequency and total implantations were significantly reduced in weeks 4 through 8 in the high-dose group, the authors concluded that there was little evidence of mutagenicity and that the reduction in implantations was due to infertility in the males. Similarly, there was no evidence for dominant lethal effects in mice exposed by inhalation to 30, 100 or 300 ppm (93, 311 or 934 mg/m^3) 2-methoxyethanol, 6 hours/day, 5 days/week for 13 weeks (Rao et al., 1983). Chapin et al. (1985a) orally dosed F344 rats with 50, 100 or 200 mg 2-methoxyethanol/kg/day for 5 days and concluded that 2-methoxyethanol is only a very weak dominant-lethal agent as evidenced by an increase in preimplantation loss in the high-dose group. In summary, it is apparent that 2-methoxyethanol is not a significant genotoxic agent, as effects are seen only at high doses or are the result of nongenetic mechanisms.

5.3. TERATOGENICITY

Horton et al. (1985) examined the developmental phase specificity and dose-response characteristics of 2-methoxyethanol-induced embryotoxicity in CD-1 mice. Approximately 10 dams/group received 2-methoxyethanol in water by gavage at designated times during gestation at dosages of 0, 100, 175, 250, 300, 350, 400, 450 or 500 mg/kg/day. All dams were sacrificed on gestation day 18 for fetal examinations. Multiple doses of 250 mg 2-methoxyethanol/kg/day given on gestation days 7-9, 8-10, 9-11, 7 and 8, 9 and 10 or 10 and 11, as well as single doses of 500 mg/kg 2-methoxyethanol on gestation days 9, 10 or 11 resulted in significant embryotoxicity as measured by reduced gestation day 18 fetal weights and embryolethality, as manifested by a significantly increased percentage of implantations resorbed. No evidence of maternal toxicity was observed. Phase-specific teratogenic effects were evident in mice receiving 250 or 500 mg 2-methoxyethanol/kg/day at various intervals between gestation days 7 and 14. Exencephaly was the predominant lesion following exposure during the early stages of gestation (gestation days 7-10), whereas paw malformations (syndactyl, oligodactyly and stunted digit number 1) were evident primarily during later stages of development, reaching a maximum after administration on gestation day 11. A dose-response experiment using single doses of 2-methoxyethanol on gestation day 11 established no-observed effect doses of 100 and 175 mg/kg for the induction of digit malformations and fetal weight reduction, respectively. At doses of $\geq$250 mg/kg, malformations and reductions in fetal body weight occurred concurrently.

Timed-pregnant rats were treated by gavage with 2-methoxyethanol in water at 0, 50 or 100 mg/kg/day on gestation days 9-15 and examined on days 16 and 21 (Toraason et al., 1985b). The high dose caused resorption of all fetuses, while the 50 mg/kg group had significantly reduced litter size and fetal body weight as well as increased visceral abnormalities in live fetuses. 2-Methoxyethanol also appeared to have a dose-related effect on calcium and vitamin D metabolism in pregnant rats. On day 21, there were significant increases in serum total and ionic calcium and significant reductions in serum 1,2,5-dihydroxy vitamin D in 2-methoxyethanol-exposed dams compared with water-treated controls.

Time-mated CD-1 mice (50/group) were orally dosed on days 7-14 of gestation with 1400 mg/kg/day (the estimated LD_{10}). Of the 30 surviving pregnant mice, all had their litters resorbed in utero (Smith, 1983).

Doe et al. (1983) reported adverse reproductive effects in rats following inhalation of 2-methoxyethanol. Groups of 20 pregnant Wistar rats were exposed to air, 100 or 300 ppm (311 or 934 mg/m^3) 2-methoxyethanol for 6 hours/day during gestation day 6-17 and were allowed to deliver their litters. Exposure to 300 ppm 2-methoxyethanol caused a significant reduction in body weight gain, and none of these rats produced litters. Only 9/20 rats exposed to 100 ppm produced litters, and there was a significant reduction in the total number of pups, the proportion of live pups at birth and the proportion surviving to 3 days postpartum. In addition, the gestation period in the 100 ppm group was significantly extended compared with control rats.

In a similar study, groups of 15 pregnant Wistar rats were treated subcutaneously with 0, 40 or 250 $\mu\ell$/kg/day (equivalent to 0, 39 and 241 mg/kg/day) 2-methoxyethanol on days 6 through 20 of gestation (Doe, 1984). The high dose resulted in piloerection and vaginal bleeding as well as significantly reduced body weight gain in the dams. None of these rats produced viable litters. Exposure to 40 $\mu\ell$/kg/day reduced the number of litters as well as the number of live pups/litter and the percentage of pups surviving for 4 days. Thus, 2-methoxyethanol is clearly fetotoxic even at relatively low doses.

Significant embryotoxicity was reported by Nagano et al. (1981) following gavage administration of 2-methoxyethanol in water at doses of 0, 31.25, 62.5, 125, 250, 500 or 100 mg/kg/day to groups of 21-24 JCL-ICR mice on gestation days 7-14. Mice were sacrificed on day 18 of gestation for dam and fetal examination. Maternal body weight gain was reduced in the 250, 500 and 1000 mg/kg groups, while marked leukopenia of the dams occurred at the highest dose. All fetuses but one of the 500 mg/kg group were dead at the two highest dose levels, while there was a 50% incidence of fetal death in the 250 mg/kg group. Gross abnormalities such as exencephaly, umbilical hernia and abnormal digits were evident in the 250 mg/kg group while fetal weight reductions were reported in the 125 and 250 mg/kg dose groups. Skeletal malformations were observed at dosages $\geq$62.5 mg/kg while skeletal variants and delayed fetal development were evident in all treated groups.

Pregnant Wistar rats were given 0.165 or 0.330 mℓ/kg 2-methoxyethanol (equivalent to 159 and 318 mg/kg, respectively) orally or intraperitoneally on gestation day 12 and were sacrificed on day 20 (Ritter et al., 1985). Embryotoxicity, calculated as the sum of dead, resorbed and malformed fetuses divided by total implantations, increased in a dose-related manner. The low-dose groups had a 65.0 (intraperitoneal) and 53.8% (oral) incidence of embryotoxicity, while both high-dose groups had a 100% incidence, malformations in these fetuses consisted predominantly of hydronephrosis, heart defects and short limbs and tails. Equimolar doses of methoxyacetic acid, a metabolite of 2-methoxyethanol, produced a similar pattern of defects suggesting that it may be the proximate teratogen.

Electrocardiography was used to evaluate heart function in 20-day fetuses following treatment of pregnant Sprague-Dawley rats with 2-methoxyethanol in water at doses of 0, 25, 50 or 100 mg/kg/day (n=11 for controls;

n=8 for treated rats) by gavage on gestation day 7-13 (Toraason et al., 1985a). The high-dose group had a 100% resorption rate early in gestation and were excluded from further examination. There was a dose-related increase in the incidence of cardiovascular defects in fetuses from dams treated with 25 or 50 mg/kg/day with ventricular septal defects being the most common. The predominant EKG abnormality was a prolonged QRS wave, which suggests the presence of an intraventricular conduction delay in fetuses. There did not appear to be any correlation between EKG abnormalities and any specific morphological defects.

In a preliminary study, pregnant monkeys (Macaca fascicularia, one/dose) were given 0.1-0.5 mℓ/kg 2-methoxyethanol by stomach tube on various days during gestation (Scott, 1984). Following a dose of 0.5 mℓ/kg (482 mg/kg) on gestation day 26 and 27, pregnancy continued normally until the conceptus was aborted on day 48, an effect considered to be compound-related. Another monkey received a 0.25 mℓ/kg 2-methoxyethanol (241 mg/kg) on days 28-31 of pregnancy. A smaller than normal fetus was delivered on gestation day 100 with one malformation, a severe kink in the tail, which was attributed to 2-methoxyethanol treatment. A third animal received 0.1 mℓ/kg (96 mg/kg) beginning on gestation day 23, and the conceptus was aborted on day 27. In summary, the author indicated that 2-methoxyethanol is teratogenic and embryolethal in monkeys, despite the limited scope of the study.

Groups of 15-20 pregnant Sprague-Dawley rats were exposed by inhalation to 25 ppm (78 mg/m^3) 2-methoxyethanol, 7 hours/day during gestation day 7-13 or 14-20 (Nelson et al., 1984a). An equal number of sham-exposed controls were included for both periods of gestation. In addition, five dams were not handled at all so that the effects of handling during gestation on the reproductive effects could be determined. There were no treatment-related differences in maternal indices, including weight gain, feed consumption, water intake, number or proportion of live offspring or pregnancy duration. Likewise, no treatment-related alterations in weight gain were observed in the offspring. Results of behavioral testing, which included ascent, rotorod, open field, activity wheel, avoidance conditioning and operant conditions tests, indicated that the only significant difference from controls was impaired avoidance conditioning in offspring from dams exposed on days 7-13. Significant ($p<0.05$) neurochemical deviations in the brains from 21-day-old offspring from all maternally-exposed groups were observed compared with sham-exposed controls, however, most notably in the brainstem and cerebrum. These included changes in acetylcholine, dopamine, 5-hydroxytryptamine and norepinephrine. There were no significant differences between sham-exposed controls and those controls that were not handled. Thus, it appears that the neurochemical effects were not due to handling. In addition, similar results were obtained in offspring produced from the mating of unexposed virgin female rats and males exposed for 6 weeks before mating to 2-methoxyethanol at a concentration of 25 ppm, 7 hours/day, 7 days/week. There were no male controls. That the results in offspring of males exposed before mating were similar to those in offspring of females exposed during gestation is surprising and cannot be explained by any known mechanism. As no significant differences were found between offspring of sham-exposed and nonhandled female controls, however, it is unlikely that the effects observed in the offspring of the males was an artifact of handling.

In a related study, groups of 8-34 pregnant Sprague-Dawley rats were exposed by inhalation to 0, 50, 100 or 200 ppm (0, 156, 311 and 622 mg/m^3) 2-methoxyethanol 7 hours/day on gestation days 7-15 (Nelson et al., 1984b).

The dams were sacrificed on day 20 for fetal removal and examination. Signs of overt toxicity in the dams were not observed in any of the treatment groups. 2-Methoxyethanol was highly embryotoxic, resulting in complete resorptions at 200 ppm and dose-related increases in resorptions and reductions in fetal weights at 50 and 100 ppm. The incidence of visceral malformations, particularly cardiac anomalies, was significantly greater in the 100 ppm group compared with controls. Skeletal malformations and variations as well as visceral variants were increased in the 50 and 100 ppm groups indicating that 2-methoxyethanol was teratogenic and caused growth retardation in the rat at these doses.

A comparative study evaluating the teratogenic potential of 2-methoxyethanol was conducted by Hanley et al. (1984) using rats, mice and rabbits. Groups of 24-32 timed-pregnant Fischer 344 rats, CF-1 mice and New Zealand White rabbits were exposed 6 hours/day to vapor concentrations of 0, 3 ppm (rats and rabbits only), 10 or 50 ppm (0, 9, 31 or 156 mg/m^3) 2-methoxyethanol on gestation days 6-15 (rats and mice) or 6-18 (rabbits). All animals were sacrificed on day 18 (mice), 21 (rats) or 29 (rabbits) at which time maternal and fetal examinations were conducted. In rats, there was an initial transient decrease in maternal body weight gain and hematological effects at 50 ppm. No differences were observed in litter sizes, resorption rate and fetal weights or lengths. Similarly, there were no dose-related differences in the incidence of malformations among exposed rats. At 50 ppm, there was a significant increase in the incidence of two minor skeletal variations (lumbar spurs and delayed ossification of the vertebral centra), considered to be indicative of slight fetotoxicity. There were no fetal effects observed among rats at 3 or 10 ppm.

A similar pattern of response was reported in mice. A slight transient body weight gain decrease in the 50 ppm group was the only observable maternal dose-related effect. Teratogenic effects were not indicated in any treatment group nor were there any treatment-related effects on reproductive parameters. Slight fetotoxicity was observed only in the 50 ppm group manifested as an increase in the incidence of extra lumbar ribs and unilateral testicular hypoplasia.

Rabbits were substantially more susceptible to the effects of 2-methoxyethanol. Maternal weight gain was decreased in the 50 ppm group and liver weights were significantly elevated at sacrifice at this dose level. Reproductive data indicated an elevated resorption rate and depressed fetal weights in the high-dose group compared with controls. The resorption rate was also significantly increased at 10 ppm, although this may be a statistical artifact based on an unusually low concurrent control value. Malformations were quite prevalent in the 50 ppm group, with 63% of the fetuses examined having at least one malformation. External, visceral and skeletal defects were significantly increased in this treatment group. Minor fetal variations, particularly those indicative of retarded development were also observed among fetal rabbits exposed to 50 ppm. In contrast, no treatment-related fetal malformations or variations were observed in the 3 and 10 ppm groups. Thus, significant indications of fetotoxicity, embryolethality and teratogenicity were manifested following exposure to 50 ppm while no treatment-related effects were evident at lower doses.

5.4. OTHER REPRODUCTIVE EFFECTS

Several studies have demonstrated that 2-methoxyethanol impaired reproductive performance in several species. In a continuous breeding study, groups of CD-1 mice (20 males and 20 females/group) were exposed to 0, 0.5, 1.0 or 2.0% 2-methoxyethanol in the drinking water during a 7-day premating period and a 14-week cohabitation period (Gulati et al., 1985). These treatments were extremely toxic, resulting in the death of all high-dose animals within 11 weeks, while 29 and 6 of the mid- and low-dose animals, respectively, died during treatment. None of the breeding pairs in the three-dose groups delivered any litters. A follow-up study using crossover matings to determine which sex had compromised reproductive performance resulted in a fertility index of 0% for females and 6% for males treated with 0.5% 2-methoxyethanol. Based on these results, 2-methoxyethanol was designated by the authors as a potent reproductive toxicant in mice at the 0.5% dose level, a dose ~779 mg/kg/day in males (based on average daily water consumption and mean body weight data).

Groups of 20-30 male and female Sprague-Dawley rats were exposed to 0, 30, 100 or 300 ppm (0, 93, 311 or 934 mg/m^3) 2-methoxyethanol vapor, 6 hours/day, 5 days/week for 13 weeks (Rao et al., 1983). Following exposure, treated animals were mated with unexposed animals to assess reproductive capability. Body weight gains were significantly decreased in the 300 ppm male and female groups while the other groups had normal weight gains. While the fertility indices of males exposed to 30 and 100 ppm were normal, the fertility of high-dose males was significantly compromised; only 20% of the untreated females were impregnated. The confirmed pregnancies ended in complete resorption of all conceptuses. 2-Methoxyethanol-induced decreased fertility was partially reversible, as 50% of the males were able to sire viable litters 13-19 weeks after the exposure period. The fertility indices for all treated females were considered comparable to control values, although there was a modest (statistically insignificant) decrease in fertility in the high-dose females, which was not considered to be treatment-related. All reproductive parameters including litter size, average pup weight up to day 21, sex ratio and survival of pups to day 21 were within control values in all treatment groups.

Testicular toxicity manifested as atrophy and impaired functional capabilities is perhaps the most well-documented effect of 2-methoxyethanol exposure. Continuous exposure to 0.5% 2-methoxyethanol in the drinking water (reportedly equivalent to 779 mg/kg/day) for 19 weeks resulted in a significant decrease in right epididymis, right testis and seminal vesicle weights at necropsy in a group of 20 CD-1 mice (Gulati et al., 1985). A detailed histopathological examination revealed atrophic testes in 80% of the treated animals. Lesions included tubular degeneration, interstitial cell hyperplasia in the testes, reduction of sperm content and accumulation of fluid and degeneration of duct epithelial cells in the epididymis. A marked loss of spermatozoa, spermatids, spermatogonia and spermatocytes, as well as epithelial cell vacuolization was also observed. There were no significant gross or histopathological changes in the reproductive organs of female mice that underwent similar treatment.

Nagano et al. (1979) administered 2-methoxyethanol at 0, 62.5, 125, 250, 500, 1000 or 2000 mg/kg/day by gavage, 5 times/week for 5 weeks to groups of five JCL-ICR mice. Animals were sacrificed the day after the last dose and histological specimens prepared. Significant dose-related reductions in absolute and relative testes weight occurred in those animals given $\geq$250 mg/kg. Varying dosage-related degrees of semeniferous tubule atrophy and decreasing spermatogenesis were observed in the testes of these animals.

Reduced mean testes weight and severe testicular atrophy characterized by disruption of the architecture of the semeniferous tubules and degenerative changes in the spermatocytes were reported by Grant et al. (1985) in F344 rats treated orally with 2-methoxyethanol in water at 500 mg/kg/day for 4 consecutive days. These effects persisted up to 22 days following the cessation of exposure. The testes of animals given 100 mg/kg day were similar in weight and morphology to those from control animals.

Foster et al. (1983) investigated the dose-response relationship between testicular damage and oral ingestion of 2-methoxyethanol as well as the temporal development and cell site of the lesion. Sprague-Dawley rats (36/treatment group) received 2-methoxyethanol in water orally at dosages of 0, 50, 100, 250 or 500 mg/kg/day. Six animals from each group were sacrificed 6 and 24 hours after a single dose while remaining groups received repeated daily doses and were killed after 2, 4, 7 and 11 days. The first significant decrease in testes weight occurred in the high-dose group after 2 days and became more pronounced at later time points. The only other significant decrease in testicular weight was in the 250 mg/kg group at 7 days. Seminal vesicle weights decreased somewhat in the higher dose groups, but no statistically significant changes were evident that were related to dose or time. Histopathological analysis of the testes revealed damage 11 days after treatment with doses ≥100 mg/kg. Results indicated that primary spermatocytes undergoing pachytene development constituted the initial and major site of morphological damage (Creasy and Foster, 1984). The authors concluded that the order of spermatocyte susceptibility to 2-methoxyethanol is dividing spermatocytes > early-pachytene spermatocytes > late-pachytene spermatocytes > mid-pachytene spermatocytes.

Oral treatment of animals with 2-methoxyethanol for 4 days at a dose level of 400 mg/kg/day produced widespread degeneration and depletion of pachytene spermatocytes and a marked decrease in testes weight. A recovery study demonstrated that testes weights and full spermatogenesis did not return to control values until 8 weeks after cessation of treatment (Foster et al., 1983). Administration of methoxyacetic acid at a dose of 592 mg/kg/day (equimolar to 500 mg/kg/day of 2-methoxyethanol) for 4 days produced damage of a similar severity and nature to that induced by 2-methoxyethanol, suggesting that the acetic acid derivative may be the active species (Foster et al., 1983).

The administration of 250 mg/kg 2-methoxyethanol by intraperitoneal injection to Sprague-Dawley rats produced tubular lesions similar to those described above (Moss et al., 1985). Primary spermatocytes in the early and late pachytene stages of development exhibited substantial necrosis and degeneration 24 hours after dosing. Pretreatment with 400 mg/kg pyrazole (intraperitoneal, 1 hour before 2-methoxyethanol dosing) provided protection against this damage, indicating that metabolic activation is necessary for 2-methoxyethanol to exert its effects on the male reproductive system.

The testicular effects of 2-methoxyethanol were also investigated by Chapin et al. (1985a,b). Groups of twelve F344 rats were treated orally with 2-methoxyethanol in water at 0, 50, 100 or 200 mg/kg/day for 5 days. Sperm assessments were conducted at weekly intervals for 8 weeks following dosing. There were time- and dose-related decreases in sperm concentration and motility, primarily in the 100 and 200 mg/kg groups, as well as concurrent elevations in the number of abnormal sperm forms in the epididymus (Chapin et al., 1985a). Histologically, the testes of the 100 and 200 mg/kg groups exhibited widespread damage and cell death at week 1, which recovered somewhat during the course of the study. Rete testis fluid protein levels were elevated only in the high-dose group, reaching a maximum at week 4 and returning to control values by week 6. Changes in cell-specific enzymes (ß-glucuronidase, sorbitol dehydrogenase and lactate dehydrogenase) were dose-related and generally reflected the number of germ cells present in the testis (Chapin et al., 1985b).

These authors also investigated the target cell for 2-methoxyethanol toxicity using F344 rats treated with 150 mg 2-methoxyethanol/kg/day per os, 5 days/week and sacrificed 1, 2, 4, 7 or 10 days after the first dose (Chapin and Lamb, 1984). The histological and biochemical data suggested, as other investigators have reported, that early and late spermatocytes are the primary targets for 2-methoxyethanol in the testis, while Sertoli cells remain relatively unaffected.

Studies using hamsters or guinea pigs revealed the occurrence of testicular atrophy similar to that observed in mice (Nagano et al., 1984). A significant decrease in mean testicular weight in Syrian golden hamsters given 62.5-500 mg/kg/day or in guinea pigs given 250 or 500 mg/kg/day, 5 days/week for 5 weeks was observed in all dose groups. These authors also reported a >4.5-fold decrease in mean testis weight in JCL-ICR mice administered 2.5% 2-methoxyethanol in the drinking water for 18 days.

Mice (B6C3F1) and rats (F344) were used by Miller et al. (1981) to assess the testicular effects of 2-methoxyethanol inhalation at concentrations of 0, 100, 300 or 1000 ppm (0, 311, 934 or 3112 mg/m^3), 6 hours/day for a total of 9 days over an 11-day period. Relative and absolute testes weight in rats and mice was markedly lower only in the 1000 ppm group. Rats but not mice were examined histologically. Histopathologically, there were severe changes in the germinal epithelium in the testes consisting of diffuse, active degeneration and necrosis of all spermatogenic elements.

After the exposure period, sperm were still present in the epididymides, but active spermatogenesis had ceased. Similar but less pronounced changes also occurred in some animals in the 300 ppm treatment group.

Groups of 10 Wistar rats were exposed to air (controls), 100 or 300 ppm (311 or 934 mg/m^3) 2-methoxyethanol for 6 hours/day for 10 consecutive days and sacrificed 1 day after the last exposure. While no effects were seen in the 100 ppm group, the testes of the rats exposed to 300 ppm 2-methoxyethanol were flacid, reduced in size and substantially lighter than the controls. Pronounced tubular atrophy was observed in the testes from all rats in the high-dose group, in which 70-100% of the semeniferous tubules were affected (Doe et al., 1983).

The dose-response relationship of the effect in the testes of a single inhalation exposure to 2-methoxyethanol and the time course of the onset of testicular damage were determined by Samuels et al. (1984). Groups of 20 Alpk/AP rats were exposed for 4 hours to 2500, 1250, 625, 300 or 150 ppm (7780, 3890, 1945, 934 or 467 mg/m^3) 2-methoxyethanol and killed 14 days after treatment. A significant reduction in testis weight was noted in rats exposed to $\geq$1250 ppm, while epididymal weights were depressed only in the highest dose group. Histopathological examination revealed dose-related bilateral tubular atrophy with disordered spermatogenesis in animals exposed to 1250, 2500 or 5000 ppm 2-methoxyethanol. Minimal degenerative changes were also seen in the testes of rats exposed to 625 ppm.

In the time-course study, groups of 90 Alpk/AP rats were exposed to 0, 1000 or 2500 ppm (0, 3112 or 7780 mg/m^3) 2-methoxyethanol vapor for a single 4-hour period. Ten rats/group were killed on days 1, 2, 3, 4, 5, 8, 10, 15 or 19 following exposure for histopathological examination. A significant dose-related decrease in testes weight as seen beginning 48 hours after exposure to either dose level and recovery was not evident by day 19. These data suggest that the primary target of 2-methoxyethanol in the testis is rapidly dividing cells as primary spermatocytes are being affected initially (Samuels et al., 1984).

Subchronic exposure to 2-methoxyethanol vapor in rats and rabbits produces a similar lesion pattern in the testes (Miller et al., 1983b). Exposure of Sprague-Dawley rats (n=10) and New Zealand White rabbits (n=3-5) to 0, 30, 100 or 300 ppm (0, 93, 311 or 934 mg/m^3) 2-methoxyethanol, 6 hours/day, 5 days/week for 13 weeks resulted in significantly lower relative testes weights compared with controls in the high-dose groups in both species. Histopathological observations in these animals revealed severe to moderate bilateral degeneration of the testicular germinal epithelium. Similar but less severe testicular changes were found in 3/5 rabbits exposed to 100 ppm 2-methoxyethanol. At 30 ppm, 1/5 rabbits had degenerative changes in the testes and 2/5 had reduced testicular size. No testicular effects, however, were observed in groups of 10 New Zealand white rabbits exposed to 0, 3, 10 and 30 ppm (9.3, 31 or 93 mg/m^3), 6 hours/day, 5 days/week for 13 weeks in another study by these investigators (Miller et al., 1982).

When rats treated as above were sacrificed 23 weeks postexposure, similar results were obtained (Rao et al., 1983). A significant decrease in the absolute and relative testes weight was observed only in the 300 ppm treatment group. Microscopic lesions interpreted to be residual effects of 2-methoxyethanol exposure were present in the testes and epididymides of 75% of those rats and included bilateral testicular degeneration characterized by atrophic semeniferous tubules.

A cross-sectional epidemiological study examined hormone levels (follicle stimulating hormone, luteinizing hormone and testosterone), hematological indices, sperm counts or numbers of abnormal sperm in employees (6 potentially exposed and 9 nonexposed workers) engaged in the manufacture and packaging of 2-methoxyethanol. This study initially included 40 exposed and 25 nonexposed workers; however, due to vasectomy and other related problems, only 6 exposed and 9 nonexposed workers were evaluated. Personnel monitoring in the production area revealed an 8-hour TWA of $\leq$0.42 ppm (1.3 mg/m^3) of 2-methoxyethanol, while the packaging and distribution areas revealed 2-hour TWA of 5.4-8.5 ppm (16.8-26.5 mg/m^3) and area atmospheric levels were between 4 and 20 ppm (12 and 62 mg/m^3) (Cook et al., 1982). No differences were observed between exposed and control workers. However, given the inadequate sample sizes and minimal methodological detail, the data from this study is of minimal value in establishing NOEL/LOEL levels.

5.5. CHRONIC AND SUBCHRONIC EFFECTS

Pertinent data regarding chronic oral or inhalation exposure to 2-methoxyethanol in animals could not be located in the available literature as cited in the Appendix; however, several subchronic and shorter-term studies describe toxic effects.

Oral studies using rats and mice are $\leq$4 weeks in duration. Groups of five male JCL-ICR mice were injected orally with doses of 2-methoxyethanol of 0, 62.5, 125, 250, 500, 1000 or 2000 mg/kg/day, 5 times/week over a period of 5 weeks (Nagano et al., 1979). The mice were examined for testicular effects, which occurred at $\geq$250 mg/kg/day (see Section 5.4.), and hematological effects. The most striking hematological effect was a sharp decrease in the white cell count in those mice given ≥500 mg/kg/day. A more modest decrease in hemoglobin and red cell count was observed in mice given 1000 or 2000 mg/kg/day.

House et al. (1985) examined the possible alterations in immune function and host resistance of B6C3F1 mice following exposure to 2-methoxyethanol or methoxyacetic acid administered by gavage in 10 doses over a 2-week period at total dosages of 250, 500 or 1000 mg/kg/day. While body and spleen weights were not altered in any treatment group, thymus weights were reduced up to 48% at the intermediate and high doses of both compounds. No significant variations in immune function or host resistance to Listeria monocytogenes were observed in animals exposed to either compound.

In dose-finding investigation designed to determine suitable doses for a reproductive toxicity study (see Section 5.4.), groups of eight male and eight female CD-1 mice were administered 2-methoxyethanol in the drinking water at levels of 0, 0.25, 0.5, 1.0, 2.5 and 5.0% for 2 weeks (Gulati et al., 1985). During treatment, five male and seven females from the high-dose group died. Animals in the 0, 0.25, 0.5 and 1.0% groups had weight gains between 8 and 11%, while the 2.5 and 5.0% groups exhibited weight losses of 16 and 35%, respectively. In addition, a dose-related decrease in the average daily consumption of water containing 1.0-5.0% 2-methoxyethanol was observed during the treatment period.

Groups of 10 CD-1 female mice were administered 2-methoxyethanol by gavage at dose levels of 190, 380, 760, 1520 and 3045 mg/kg/day for 8 consecutive days, followed by an 8-day observation period in a study designed to determine the maximum tolerated dose (Smith, 1983). All animals in the highest dose group died during the dosing period and two animals administered 1520 mg/kg/day died on the last dosing day. There was no significant difference in mean body weight gain among the surviving treated and control groups throughout the study.

In a study of testicular effects (see Section 5.4.), male Sprague-Dawley rats (36/group) received 2-methoxyethanol per os at dosages of 50, 100, 250 and 500 mg/kg/day for up to 11 days (Foster et al., 1983). Reductions in body weight gain were limited to the high-dose animals after 11 days of treatment. Decreased relative liver weight was observed in all but low-dose rats 24 hours after the first dose. These reductions persisted in the 250 and 500 mg/kg/day groups through day 7 but returned to control levels by day 11. Rats treated with 2-methoxyethanol for 4 days at a dose level of 500 mg/kg/day initially exhibited a marked decrease in relative liver weight; however, liver weights returned to normal after a 2-week recovery period. There were no histological or ultrastructural liver abnormalities at any dosage used in this study.

Grant et al. (1985) studied the effects of 2-methoxyethanol in the hematopoietic system of male F344 following 4 consecutive days of treatment with 100 and 500 mg 2-methoxyethanol/kg/day given orally. One day after the final dose, there were generally dose-related reductions in relative kidney, spleen and thymus weights. By day 22 of recovery, all organ weights were similar to those of the control group. Liver weight was not affected at either dose level. In the high-dose group, 1 day after treatment, femoral bone marrow was extensively hemorrhagic and appeared to be associated with extensive thinning of the sinus endothelial cells; however, normal marrow architecture was restored by day 4 of recovery. 2-Methoxyethanol also abolished splenic extramedullary hematopoiesis at 500 mg/kg/day but returned to normal by day 22. The major hematological effect of 2-methoxyethanol was leukopenia, which was apparently associated with reductions in both lymphocytes and neutrophils. Leukocyte counts failed to reach control values by the end of the recovery period. A mild normochromic, normocytic anemia was evident up to 8 days after dosing but was reversible by day 22.

Two subchronic inhalation studies were available. Werner et al. (1943a) exposed two dogs to 750 ppm (2334 mg/m^3) 2-methoxyethanol, 7 hours/day, 5 days/week for 12 weeks and observed them for an additional 7 weeks before sacrifice. Except for moderate ocular and nasal irritation, the most significant changes occurred in the blood. A maximal decrease (~38%) in red cell count, cell volume and hemoglobin concentration, indicative of microcytic anemia, occurred after 4-6 weeks of exposure and persisted throughout 12 weeks. There was a 7-fold increase in the number of immature granulocytes while the red cells showed an increased hypochromia, polychromatophilia and microcytosis. No effects on urinalysis and clinical chemistry parameters and no histological lesions in major organs were observed.

Miller et al. (1983b) reported the subchronic inhalation toxicity of 2-methoxyethanol in Sprague-Dawley rats and New Zealand White rabbits. Males and females of both species (10 rats and 5 rabbits of each sex/group) were exposed to 0, 30, 100 and 300 ppm (0, 93, 311 and 934 mg/m^3) 2-methoxyethanol, 6 hours/day, 5 days/week for 13 weeks. Four rabbits (two male and two female) in the 300 ppm group were found dead or were sacrificed when moribund during the course of the study, although the relationship to 2-methoxyethanol exposure was uncertain. Decreased body weight gains were evident in female rats in the 300 ppm group after 3 weeks of exposure, while in the male high-dose group, this decrease became significant after 5 weeks. A moderate reduction in mean body weights occurred in female rats exposed to 100 ppm following 7 weeks of exposure. Although mean body weights for male and female rabbits in the 300 ppm group and for female rabbits in the 100 ppm group were somewhat lower than controls, these differences were not statistically significant. Mean thymus weight was significantly reduced in all high-dose animals while alterations in mean liver weight were not considered treatment-related. Hematological changes were apparent after 4 weeks of exposure in both rats and rabbits as evidenced by decreased mean white blood cell counts, platelet counts, packed cell volumes, hemoglobin concentrations and red blood cell counts (rabbits only).

Gross pathology was limited in rats to the high-dose animals and included decreased thymus size in both sexes and decreased abdominal adipose tissue in some females. In high-dose male and female rabbits, there was decreased abdominal fat, decreased thymus size and reduced amounts of lymphoid tissue. Microscopic lesions included thymic atrophy manifested primarily as a decrease in cortical lymphocytes in high-dose rats and lymphoid atrophy of the thymus and cecal appendix in rabbits exposed to 100 and 300 ppm. Gross and histopathological effects on the testes of male rats and rabbits were discussed in Section 5.4.

Adult male and female Wistar rats (n=23) were exposed to 310 ppm (965 mg/m^3) 2-methoxyethanol, 7 hours/day, 5 days/week for 5 weeks. Animals were sacrificed throughout the exposure period and up to 3 weeks following the cessation of exposure. No significant changes in body weight or mortality were noted at any time point during the study. Similarly, there were no differences in lung, kidney or heart parameters compared with controls. In the spleen, there was a doubling of the hemosiderin content and a significant replacement of bone marrow cells with fatty tissue. Additionally, the proportion of juvenile granulocytes in the blood was significantly increased relative to control animals. This increase was obvious after only 1 week of exposure. The pathological and hematological variations were generally reversible after termination of exposure (Werner et al., 1943b).

Doe et al. (1983) exposed groups of 10 male Wistar rats to 0, 100 or 300 ppm (0, 311 or 934 mg/m^3) 2-methoxyethanol vapor, 6 hours/day for 10 consecutive days. Reproductive and testicular effects were presented in Section 5.4. Body weight gain in the high-dose group was significantly reduced throughout treatment. In addition, the thymus glands of 9/10 of the 300 ppm group were reduced in size as noted at postmortem examination. This group also had statistically significant reduction in white blood cell count, red blood cell count, hemoglobin concentration, hematocrit and mean corpuscular hemoglobin. Rats exposed to 100 ppm were clinically indistinguishable from the controls.

Miller et al. (1981) exposed male and female Fischer 344 rats and B6C3F1 mice to 0, 100, 300 or 1000 ppm (0, 311, 934 or 3112 mg/m^3) 2-methoxyethanol vapor, 6 hours/day for a total of nine exposures during an 11-day interval. Body weight gain was significantly retarded in female rats receiving $\geq$100 ppm and in male rats receiving 300 or 1000 ppm. The growth of the mice was not significantly altered at any dose level. Dose-related decreases in thymus weight were observed in both species with significant reductions occurring in all animals exposed to 1000 ppm and in male and female rats as well as female mice in the 300 ppm group. Of the various hematological indices, the white blood cell counts of both rats and mice were most severely altered, especially at the 1000 ppm dose level. Other altered parameters at this dose included depressed packed cell volume, red blood cell counts and hemoglobin concentration in both male and female rats and male mice. White blood cell counts were also depressed in male rats at 100 and 300 ppm and female rats exposed to 300 ppm. Osmotic red blood cell fragility of male and female rats exposed to 1000 ppm was not significantly different from control animals. Microscopic lesions were evident in all but the low-dose rats and included a marked reduction in bone marrow cellularity, severe lymphoid depletion in the cortex of the thymus and reduced numbers of lymphoid cells in the spleen and mesenteric lymphic nodes of the 1000 ppm groups and a moderate reduction in thymic cortical lymphoid cells in the 300 ppm groups. Mice were not examined histopathologically.

Inhalation of 125 ppm (389 mg/m^3) 2-methoxyethanol, 4 hours/day for 7 days caused rats to exhibit a decrease in pole climbing response, the severity of which increased with successive exposures (Goldberg et al., 1962).

The neurotoxicity of 2-methoxyethanol was investigated by Savolainen (1980) in male Wistar rats by studying the effects on cerebral glial cell biochemistry following exposure to 50, 100 or 400 ppm (156, 311 or 1245 mg/m^3), 6 hours/day for 1 or 2 weeks. Isolated glial cells had significant increases in a number of biochemical parameters at all doses after both 1- and 2-week exposures. At the 400 ppm concentration, partial hindlimb paresis was observed, body weights were significantly reduced and the spleen was enlarged. The author concluded that the central nervous system is an important target of 2-methoxyethanol and that lesions may be manifested as demyelinations.

Episodes of occupational exposure suggest that hematological and neurologic deficits as well as some changes in renal function are the primary consequences of 2-methoxyethanol intoxication in humans. Donley (1936) described a case of moderate anemia and toxic encephalopathy in a female worker exposed to a solution containing 2-methoxyethanol (<3%), isopropanol (74%) and dimethyl phthalate (<3%). Symptoms and signs included headache, drowsiness, lethargy, general weakness, ataxia, irregular and unequal pupils, disorientation and some psychopathic disturbances. Similar symptoms were reported by Parsons and Parsons (1938) in two male workers exposed to

2-methoxyethanol vapors for up to 1 year. These men were found to have moderately severe anemia and granulopenia, and suffered from personality changes, frequent dizzy and fainting spells, lethargy, weakness, sleepiness, headache, hyperactivity of all reflexes, transitory right ankle clonus, burning of the eyes, persistent dilation of the pupils, gastrointestinal upset, nocturia, loss of weight and moderate ataxia. Both patients apparently recovered completely. Greenburg et al. (1938) conducted a more extensive investigation of workers at the same factory involving 19 employees who had been exposed for up to 112 weeks to a solution containing 33% 2-methoxyethanol and 67% denatured ethanol. Clinical examination revealed an altered hematological profile suggestive of macrocytic anemia associated with granulopenia and platelet reduction. All subjects suffered some degree of excessive fatigue, abnormal reflexes and tremors. In workroom air 2-methoxyethanol concentrations ranged from 25-76 ppm (78-237 mg/m^3), although the actual concentrations to which these employees were subjected were, in all likelihood, much higher because of improved ventilation conditions implemented before measurement.

Zavon (1963) reported five cases of illness in workers exposed to experimentally calculated air concentrations of 61-3960 ppm (190-12,324 mg/m^3) 2-methoxyethanol for up to 7 months. All subjects displayed anemia, with one having a hypocellular bone marrow with a decrease in the percentage of erythroid elements. Neurologic symptoms included depression, personality changes, slurred speech, ataxia, tremors, dizziness and a positive Rhomberg test. All patients recovered following improved plant hygiene in which concentrations of 2-methoxyethanol were reduced to ~20 ppm (~62 mg/m^3).

Two cases of ingestion of 100 mℓ 2-methoxyethanol (97 g) resulted in symptoms similar to those mentioned above that appeared 8-18 hours after exposure (Nitter-Hauge, 1970). Marked acidosis was observed in both cases and one patient developed oxaluria.

More recently, Ohi and Wegman (1978) reported the effects of cutaneous exposure to 2-methoxyethanol in two workers employed in an electroplating operation. Exposure over a 4- to 6-month period resulted in a typical pattern of intoxication including central nervous system effects, metabolic disturbances and hematopoietic suppression. Recovery occurred gradually following cessation of exposure.

Cohen (1984) reported the case of a microfilm worker production exposed to 2-methoxyethanol over a 19-month period. The personal breathing zone concentration averaged 35 ppm (109 mg/m^3) with a range of 18.2-57.8 ppm (57-180 mg/m^3). Reversible central nervous system and hematopoietic effects occurred following skin and inhalation exposure to 2-methoxyethanol. This study illustrates that hematopoietic and subjective neurologic symptoms may result in humans being exposed to 2-methoxyethanol at levels (~35 ppm or 109 mg/m^3) that have been associated with reproductive and teratogenic effects to animals.

5.6. OTHER RELEVANT INFORMATION

The acute effects of 2-methoxyethanol in a number of species are summarized in Table 5-2.

The effects of 2-methoxyethanol on cell-mediated immunocompetence was investigated by Houchens et al. (1984) using allogeneic B6C3F1 and syngeneic CD2F1 mice. Allogeneic mice were treated orally with 2-methoxyethanol at dosages of 300, 600 or 1200 mg/kg/day on days -12 through -8 and -5 through -1 before challenge with L1210 mouse leukemia cells. Syngeneic mice were similarly treated on days 1-5 and 8-12 after challenge with leukemia cells.

TABLE 5-2

Acute Effects of 2-Methoxyethanol*

Route	Species	Dose (g/kg)	Response	Reference
Oral	rats (male)	2.46 (50% aqueous solution)	LD_{50}; narcosis, kidney damage, liver and gastrointestinal irritation	Smyth et al., 1941
Oral	rats (male) rats (female)	3.25 3.4	LD_{50} LD_{50}	Carpenter et al., 1956
Oral	mice	2.8 (in oil; slightly lower in aqueous solution)	LD_{50}	Saparmamedov, 1974
Oral	rabbits	0.89	LD_{50}	Carpenter et al., 1956
Oral	cats	0.94	Average duration of survival = 6.8 days; symptoms: weight loss, depressed blood calcium, albuminuria, motor impairment, ataxia, somnolence, dyspnea; pathology: severe renal necropsis, myocarditis, hepatitis, gastroenteritis	Doerr et al., 1947
Oral	guinea pigs	0.95	LD_{50}; narcosis, kidney damage, liver and gastrointestinal irritation	Carpenter et al., 1956; Smyth et al., 1941
Injection (route not specified)	rabbits	2.3/day x 2	No increase in urinary oxalic acid; renal tubular degeneration; testicular degeneration; hyperemia of liver and spleen	Wiley et al., 1938
Injection (route not specified)	dogs	5.8/day x 3	No increase in urinary oxalic acid; liver markedly hyperemic; calcified casts in pyramidal tubules of kidney; edema of the bladder wall	Wiley et al., 1938
Intraperitoneal	rats (female) (Carworth-Wistar)	2.5	LD_{50}	Carpenter et al., 1956
Intraperitoneal	rats (female) (Dow-Wistar or Carworth)	0.97, two injections, 24 hours apart	Lethal dose (within 24 hours)	Goldberg et al., 1962
Intraperitoneal	rats	1.2	Average lethal dose; narcosis, urinary incontinence, respiratory distress, liver damage, peritoneal adhesions	Sanderson, 1959
Intraperitoneal	mice (female)	2.15	LD_{50} within 7 days, damage to renal tubules, spleen and lymph nodes	Karel et al., 1947

TABLE 5-2 (cont.)

Route	Species	Dose (g/kg)	Response	Reference
Intraperitoneal	mice (female)	0.1	Potentiated hexobarbital anesthesia	Goldberg et al., 1962
Intravenous	rats (female)	2.7 (0.25% in 0.75% NaCl) 2.14 (undiluted)	LD_{50}	Carpenter et al., 1956
Intravenous	rabbits	0.25-0.5	Fatty degeneration and focal necrosis in liver	Yoshida, 1961
Inhalation	rats (female)	17,601 mg/m^3 for 4 hours	60% mortality (overnight)	Goldberg et al., 1962
Inhalation	rats (male)	6224 mg/m^3 for 8 hours	Lethal dose, range-finding (within 14 days)	Carpenter et al., 1956
Inhalation	rats (male)	12,448 mg/m^3 for 4 hours	1/6 mortality, range-finding (within 14 days)	Carpenter et al., 1956
Inhalation	rats (male, female)	6224 mg/m^3 for 4 hours	2/6, 3/6, 4/6 mortality	Carpenter et al., 1949
Inhalation	rats (female)	12,448 mg/m^3 for 4 hours	Negative neurological findings (no effect on rolling roller performance)	Goldberg et al., 1962
Inhalation	rats (female)	6224 mg/m^3 for 4 hours x 7 days	Weight loss; renal and hematologic effects; no effect on motor function	Goldberg et al., 1962
Inhalation	mice	10,519 mg/m^3 for 7 hours	All dead at 32 hours after exposure	Werner et al., 1943c
Inhalation	mice	4606 mg/m^3 for 7 hours	LC_{50} within 3 weeks after exposure	Werner et al., 1943c
Inhalation	mice	12,448 mg/m^3 for 4 hours	Negative neurological findings (no effect in rolling roller performance)	Goldberg et al., 1962
Inhalation	rabbit	1.34	LD_{50}	NLM, 1981
Dermal	rabbits	1.3 undiluted (24 hours skin contact)	LD_{50} (within 14 days)	Carpenter et al., 1956
Dermal	rabbits	2.0	LD_{50}	Dow, n.d.
Ocular	rabbits	0.40	Necrosis of surface of cornea	Carpenter and Smyth, 1946
Ocular	guinea pigs	0.01	Irritation	Sanderson, 1959

*Source: NIOSH, 1982

Although no direct antitumor activity was detected, results in the allogeneic mice indicated that 2-methoxyethanol may exert a prophylactic effect by stimulating the immune system.

Young and Woolner (1946) reported the only case of human fatality following ingestion of ~240 mℓ 2-methoxyethanol (232 g). An autopsy revealed marked fatty degeneration of the liver, severe degeneration of the kidney tubules, moderate hemorrhagic gastritis and slight congestion of the lungs.

Amoore and Hautala (1983) reported an air-odor threshold for 2-methoxyethanol of 2.3 ppm and calculated an odor safety factor (TLV ÷ odor threshold) of 2.1, which indicates that <50% of distracted persons perceive warning of the TLV (5 ppm). In contrast, Rowe and Wolf (1982) reported an odor threshold of 60 ppm and a strong odor level of 90 ppm using human volunteers (levels that are substantially greater than the TLV). In another study using human volunteers, 25 ppm was considered to be the maximum tolerated odor level by 3/5 people tested, while the intolerable level appeared to be >115 ppm (Dow, n.d.).

5.7. SUMMARY

Pertinent data regarding the carcinogenicity of 2-methoxyethanol could not be located in the available literature as cited in the Appendix.

Results from several mutagenicity assays suggest that 2-methoxyethanol is not a significant genotoxic agent. Reverse mutation (Ong, 1980; McGregor et al., 1983; McGregor, 1984), DNA repair (McGregor et al., 1983), chromosome aberration (McGregor et al., 1983), sex-linked recessive lethal (McGregor et al., 1983) and point mutation (McGregor, 1984) assays were negative. Dominant lethal and sperm abnormality assays yielded some positive results (McGregor et al., 1983, Chapin et al., 1985a), although effects were observed only at high doses and it is not clear whether genetic mechanisms were involved in the response.

Acute and subchronic studies have revealed that 2-methoxyethanol mainly exerts effects on the blood, kidneys, liver, testes, spleen, central nervous system and developing fetus. Chronic studies using 2-methoxyethanol could not be located in the available literature as cited in the Appendix.

Oral and inhalation exposure to 2-methoxyethanol has resulted in fetotoxic and embryolethal effects in several species. Oral administration of 2-methoxyethanol to JCL-ICR mice at doses ranging from 31.25-1000 mg/kg/day on gestation days 7-14 resulted in fetal mortality at doses ≥250 mg/kg and decreased fetal weights at 125 and 250 mg/kg. The incidence of skeletal malformations was significantly higher in the 62.5, 125 and 250 mg/kg groups. Skeletal variations and retarded fetal ossification were evident in all treatment groups. Maternal effects included decreased weight gain in the ≥250 mg/kg groups and a decreased leukocyte count in the high-dose group. Thus, even at the lowest dose, 31.25 mg/kg, significant embryotoxic effects were observed (Nagano et al., 1981).

Phase-specific teratogenicity was elicited in CD-1 mice receiving 100-500 mg/kg 2-methoxyethanol orally during various periods between days 7 and 14 of gestation (Horton et al., 1985). Administration of 250 mg/kg/day during gestation days 7-14 resulted in gross malformations similar to those reported by Nagano et al. (1981). Exencephaly was the predominant lesion resulting from administration during the early stages of gestation (gestation days 7-9), whereas paw malformations were prevalent during later stages of development, becoming maximal on gestation day 11. Evaluation of the dose-response relationship for digit anomalies following a single dose on gestation day 11 revealed a NOEL of 100 mg/kg while malformations resulted at 175 mg/kg. At higher doses, malformations with concomitant decreases in fetal weight were observed.

The incidence of malformed fetuses (hydronephrosis, heart defects and short limbs and tails) was significantly increased in Wistar rats receiving 159 or 319 mg/kg 2-methoxyethanol on gestation day 12. Equimolar doses of methoxyacetic acid, a metabolite of 2-methoxyethanol, were similarly potent, indicating that it may be the proximate teratogen (Ritter et al., 1985). Treatment of time-mated Sprague-Dawley rats with 25, 50 or 100 mg 2-methoxyethanol/kg/day on gestation day 7-13 resulted in a 100% resorption rate in the high-dose group and an increased incidence of gross cardiovascular malformation in the 50 mg/kg group. There was a dose-related increase in EKG abnormalities at $\geq$25 mg/kg, with a prolonged QRS wave being the most prevalent aberration in both the 25 and 50 mg/kg groups (Toraason et al., 1985a).

A preliminary study in monkeys indicated that oral doses of 2-methoxyethanol as low as 97 mg/kg given during short periods of pregnancy resulted either in abortions or malformed offspring (Scott, 1984).

Teratogenic responses have also been induced following inhalation exposure. Treatment of pregnant Sprague-Dawley rats on gestation days 7-13 or 14-20 or male rats for 6 weeks with 78 mg/m^3 2-methoxyethanol, 7 hours/day resulted in significant neurochemical deviations in the brains of 21-day offspring from both maternally- and paternally-exposed groups (Nelson et al., 1984a). Alterations were most prevalent in the brainstem and cerebrum and less numerous in the cerebellum and midbrain. A significant decrease in avoidance conditioning in offspring from dams exposed on days 7-13 was the only evidence of altered behavior. No effects on maternal or paternal animals were observed (Nelson et al., 1984a). In a related study, vapor concentrations of 2-methoxyethanol, which were not maternally toxic, produced complete resorptions at 622 mg/m³ and increased resorptions, reduced fetal weights and skeletal and cardiovascular anomalies at both 311 and 156 mg/m³ when administered 7 hours/day on gestation days 7-15 (Nelson et al., 1984b). Neither study established a no-effect level for embryotoxicity.

Hanley et al. (1984a) compared the teratogenic potency of 2-methoxyethanol in CF-1 mice, F-344 rats and New Zealand White rabbits by exposing dams, 6 hours/day to 9 (rats and rabbits), 31 or 156 mg/m³ on gestation days 6-15 (rats and mice) or days 6-18 (rabbits). Offspring from rats and mice exposed to 156 mg/m³ showed no evidence of a teratogenic effect, although indications of slight fetotoxicity (minor skeletal variations) were observed in both species. Exposure in the high-dose rabbit group produced significant increases in the incidence of malformations, minor variations and resorptions as well as decreases in mean fetal body weight. Transient decreases in maternal body weight gain in all high-dose groups were the only consistent signs of maternal toxicity. No significant treatment-related effects on fetal development were observed in any species exposed to ≤31 mg/m³, 6 hours/day.

Reproductive performance and testicular function can be substantially compromised by oral or inhalation exposure to 2-methoxyethanol. Treatment of rats orally with 2-methoxyethanol on gestation days 9-15 caused 100% resorptions at a 100 mg/kg/day dose level, while 50 mg/kg/day significantly depressed litter size and fetal body weights (Toraason et al., 1985b). Total resorption was also observed in CD-1 mice following oral administration of 1400 mg/kg/day 2-methoxyethanol on days 7-14 of gestation (Smith, 1983). The lowest dose of 2-methoxyethanol (estimated by the authors to be

779 mg/kg/day for males) in a 15-week drinking water study by Gulati et al. (1985) resulted in a 1 and 6% fertility index for female and male CD-1 mice, respectively. These authors also observed marked testicular degeneration and decreased spermatogenesis in male mice treated similarly for 19 weeks.

Reduced testicular weight and tubular degeneration were evident in F344 rats treated orally with 500 mg/kg/day 2-methoxyethanol for 4 days. No testicular changes were observed in animals given 100 mg/kg/day (Grant et al., 1985). Similar effects were reported in JCL-ICR mice given $\geq$250 mg/kg/day 2-methoxyethanol by gavage, 5 times/week for 5 weeks. Animals given doses of $\leq$125 mg/kg/day exhibited no adverse effects (Nagano et al., 1979). These investigators, using the same protocol, produced testicular degeneration in Syrian golden hamsters given 62.5-500 mg/kg/day and in guinea pigs given 250 or 500 mg/kg/day (Nagano et al., 1984).

Oral ingestion of 2-methoxyethanol by Sprague-Dawley rats at dosages of 50, 100, 250 or 500 mg/kg/day for up to 11 days resulted in testicular damage characterized by primary spermatocyte lesions in all but the low-dose treatment group (Foster et al., 1983). Treatment with 500 mg/kg/day for 4 days produced widespread degeneration and decreased testis weight, effects that were reversible after 8 weeks (a period equivalent to one full maturation cycle). Similarly, F344 rats dosed orally with 100 or 200 mg/kg/day 2-methoxyethanol for 5 consecutive days exhibited time- and dose-related decreases in sperm concentration and motility as well as marked testicular degeneration. In addition, changes in testicular protein and enzyme levels were observed in these treatment groups (Chapin et al., 1985b). In both of these studies, a dose of 50 mg/kg/day did not produce significant alterations in testicular morphology or function.

Fertility was completely suppressed in male Sprague-Dawley rats exposed to 934 mg/m³ 2-methoxyethanol, 6 hours/day, 5 days/week for 13 weeks, but was partially restored at 13 weeks postexposure (Rao et al., 1983). Decreased testicular size and atrophic tubules were also observed in these animals. Female rats exposed to the same concentration did not exhibit any adverse reproductive effects. No effects on fertility and reproduction were observed at 311 mg/m³ in rats. Doe et al. (1983), however, reported adverse reproductive effects in Wistar rats exposed to 311 mg/m³, 6 hours/day during gestation day 6-17. Litter production and the number, weight and viability of the pups were reduced at this dose. Exposure to 934 mg/m³ resulted in the delivery of no litters. Male rats exposed to this same dose for 10 days experienced reduced testicular weight and tubular atrophy while a dose of 311 mg/m³ was without effect in males.

A number of effects were observed in Sprague-Dawley rats and New Zealand White rabbits exposed to 93, 311 or 934 mg/m³ 2-methoxyethanol vapor, 6 hours/day, 5 days/week for 13 weeks (Miller et al., 1983b). The high dose resulted in reduced body, thymus and testicular weights as well as hematological alterations and testicular degeneration in both species. Mortality was also increased in rabbits in the 311 and 934 mg/m³ treatment groups. Testicular alterations were observed in the mid- and low-dose rabbit groups, while rats at these doses displayed no apparent effects (Miller et al., 1983b). No testicular effects were found in rabbits similarly exposed to 0, 3, 10 or 30 ppm (0, 9, 31 or 93 mg/m³) for 13 weeks (Miller et al., 1982).

Following a single 4-hour exposure to 2-methoxyethanol vapor, a dose-related decrease in testis weight was observed in Alpk/AP rats exposed to 3890, 7780 or 15,560 mg/m³ 2-methoxyethanol. Minimal degenerative changes were seen in the testis of rats exposed to concentrations ≥1945 mg/m³ (Samuels et al., 1984).

A similar pattern of effects was reported by Miller et al. (1981) following exposure of F344 rats and B6C3F1 mice to 311, 934 or 3112 mg/m³ 2-methoxyethanol, 6 hours/day for a total of 9 days during an 11-day period. The high-dose groups displayed significant adverse effects on body weight gain, peripheral blood counts, bone marrow, testes and lymphoid tissues. Similar but less severe effects were observed at the 934 mg/m³ dose level.

Impaired reproductive capacity was the result of subcutaneous injection of 39 or 242 mg/kg/day 2-methoxyethanol on days 6-20 of gestation in Wistar rats. No litters were produced in the high-dose group, while the low-dose animals produced fewer litters than controls (Doe, 1984).

Administration of 250 mg/kg/ 2-methoxyethanol by intraperitoneal injection resulted in a depleted spermatocyte population in Sprague-Dawley rats 24 hours after dosing (Moss et al., 1985).

Nonreproductive effects of 2-methoxyethanol exposure generally involve alterations in hematology, the thymus and in the central nervous system. An altered hematological profile was elicited in Wistar rats exposed to 965 mg/m³ 2-methoxyethanol, 7 hours/day, 5 days/week for 5 weeks and dogs similarly exposed to 2334 mg/m³ for 12 weeks (Werner, 1943a,b). Male F344 rats that were given 2-methoxyethanol per os for 4 consecutive days at doses of 100 or 500 mg/kg/day exhibited dose-dependent changes in the hematological profile that were generally reversible within 3 weeks after the cessation of treatment (Grant et al., 1985). Reversible reductions in relative kidney, spleen and thymus weights were also observed. Nagano et al. (1979) reported a sharp decrease in the white cell count of JCL-ICR mice given oral doses of 2-methoxyethanol $\geq$500 mg/kg/day, 5 times/week for 5 weeks.

Similarly, Doe et al. (1983) reported significant reductions in a number of blood indices as well as depressed body weight gain and reduced thymus size in Wistar rats exposed to 934 mg/m³ 2-methoxyethanol, 6 hours/day for 10 consecutive days. Rats in a 311 mg/m³ dose group were hematologically similar to controls. Alterations in biochemical parameters in isolated glial cells from Wistar rats were observed following exposure to ≥156 mg/m³ 2-methoxyethanol, 6 hours/day for up to 2 weeks (Savolainen, 1980).

Foster et al. (1983) reported that male Sprague-Dawley rats treated orally with ≥100 mg/kg/day for 7-11 days experienced reductions in relative liver weight while animals given 50 mg/kg/day were unaffected. House et al. (1985) administered 2-methoxyethanol by gavage to B6C3F1 mice at dosages of 250, 500 or 1000 mg/kg/day, 5 days/week for 2 weeks and noted a sharp reduction in thymus weights in the mid- and high-dose groups. Increased mortality was reported by Smith (1983) in CD-1 mice after oral administration of 1520 or 3045 mg/kg/day for 8 consecutive days. This effect was also observed following the consumption of drinking water containing 5.0% 2-methoxyethanol by CD-1 mice for 2 weeks (Gulati et al., 1985). At a drinking water concentration of 2.5% mice suffered significant weight losses, while mice maintained on water containing ≤1.0% displayed no overt effects of toxicity.

Human exposure episodes have resulted in only one reported fatality following ingestion (Young and Woolner, 1946). Occupational exposure to 2-methoxyethanol vapors has generally resulted in transient hematological, neurological and renal deficits. Moderate cases of anemia and toxic encephalopathy are the signs most often reported to be the results of inhalation or dermal exposure to 2-methoxyethanol in the workplace (Donley, 1936; Parsons and Parsons, 1938; Greenburg et al., 1938; Zavon, 1963;

Nitter-Hauge, 1970; Ohi and Wegman, 1978; Cohen, 1984). Occupational exposures to concentrations of $\leq$20 ppm ($\leq$62 mg/m³) appear to result in no overt effects.

The acute toxic effects of 2-methoxyethanol generally are similar to those induced by longer term exposures with the brain, kidneys and blood being the primary target organs. Generally, 2-methoxyethanol is relatively low in acute oral toxicity, mildly irritating to the eyes, not appreciably irritating to the skin, may be absorbed through the skin but is not significantly toxic by this route and is somewhat more toxic when inhaled (Rowe and Wolf, 1982). Oral LD_{50} values range from 0.89 g/kg in rabbits to 3.4 mg/kg in female rats (Carpenter et al., 1956) while dermal LD_{50}s in rabbits range from 1.3-2.0 g/kg (Carpenter et al., 1956; Dow, n.d.). A wide range of acute inhalation exposure situations (from 1556-17,601 mg/m³) has resulted in increased mortality and renal and hematological disturbances (Goldberg et al., 1962; Carpenter et al., 1949, 1956; Werner et al., 1943c).

6. AQUATIC TOXICITY

6.1. ACUTE

The available data concerning acute toxicity presented in Table 6-1 indicate that 2-methoxyethanol is relatively nontoxic to fish and crustaceans. No LC_{50} values <1000 mg/ℓ were reported for six species of fish and two crustaceans. Limited data for three protozoans indicate that they may be more sensitive than fish and crustaceans. Toxicity thresholds for inhibition of cell multiplication were 1715 mg/ℓ for *Entosiphon subcatum* and 2.2 mg/ℓ for *Chilomonas paramecium* (Bringmann and Kuehn, 1981).

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of 2-methoxyethanol could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Bringmann and Kuehn (1980) reported that the toxicity threshold for inhibition of cell multiplication was >10,000 mg/ℓ for the green alga, *Scendesmus quadricauda*, and the bacterium, *Pseudomonas putida*. The blue-green alga, *Microcystis aeruginosa*, was more sensitive, with a toxicity threshold of 100 mg/ℓ (Bringmann and Kuehn, 1978).

6.4. RESIDUES

Pertinent data regarding 2-methoxyethanol residues in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

The available data indicate that 2-methoxyethanol is relatively nontoxic to fish and crustaceans in acute exposures. No LC_{50} values <10,000 mg/ℓ were reported for six species of fish and two crustaceans (see Table 6-1). Flagellate protozoans appeared to be more sensitive, with toxicity thresholds of 2.2 and 1715 mg/ℓ reported for *C. paramecium* and *E. subcatum*,

TABLE 6-1

Acute Toxicity of 2-Methoxyethanol to Aquatic Animals

Species	Concentration (mg/ℓ)	Effect	Reference
FISH			
Bluegill *Lepomis macrochirus*	10,000	No mortality, 96 hours	Dawson et al., 1977
Rainbow trout *Salmo gairdneri*	12,610 15,520	No mortality, 96 hours 96-hour LC_{50}	Benville, 1974
Goldfish *Carassius auratus*	>5,000	24-hour LC_{50}	Bridie et al., 1979
Guppy *Poecilia reticulata*	18,118	14-day LC_{50}	Konemann, 1981
Tidewater silverside *Menidia beryllina*	10,000 5,000 >10,000	40% mortality, 96 hours 10% mortality, 96 hours 96-hour LC_{50}	Dawson et al., 1977

TABLE 6-1 (cont.)

Species	Concentration (mg/ℓ)	Effect	Reference
CRUSTACEANS			
Water flea *Daphnia magna*	>10,000	24-hour LC_{50}	Bringmann and Kuehn, 1977
	18,678	calculated 48-hour EC_{50}, immobilization (based on K_{ow})	
Brine shrimp *Artemia salina*	>10,000	24-hour LC_{50}	Price et al., 1974
PROTOZOA			
Flagellate *Entosiphon sulcatum*	1,715	Toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1981
Chilomonas paramecium	2.2	Same as above	
Ciliate *Uronema parduczi*	>10,000	Same as above	Bringmann and Kuehn, 1981

respectively (Bringmann and Kuehn, 1981). Of the algae and bacteria tested, the blue-green alga, _M_. _aeruginosa_, with a toxicity threshold of 100 mg/ℓ, was more sensitive than the green alga, _S_. _quadricauda_, or the bacterium, _P_. _putida_, both with toxicity thresholds >10,000 mg/ℓ (Bringmann and Kuehn, 1978, 1980).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1985-1986) recently lowered the TLV for 2-methoxyethanol from 25 ppm to 5 ppm (16 mg/m^3) based upon its reported testicular effects as documented by ACGIH (1986). The lower TLV was recommended in 1982 and adopted in 1984 (ACGIH, 1986). The previous TLV of 25 ppm (~80 mg/m^3) was based on hemotological and CNS effects in humans occupationally exposed (ACGIH, 1980). OSHA has established a permissible exposure limit of 25 ppm (78 mg/m^3) (OSHA, 1985). Both of these recommendations are accompanied by the "skin" notation indicating that dermal absorption is a potentially hazardous route of exposure.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of 2-methoxyethanol could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding the carcinogenicity of 2-methoxyethanol could not be located in the available literature as cited in the Appendix.

Results from several mutagenicity assays suggest that 2-methoxyethanol is not a significant genotoxic agent. Reverse mutation (Ong, 1980; McGregor et al., 1983; McGregor, 1984), DNA repair (McGregor et al., 1983), chromosome aberration (McGregor et al., 1983), sex-linked recessive lethal (McGregor et al., 1983) and point mutation (McGregor, 1984) assays were negative. Dominant lethal and sperm abnormality assays yielded some positive results (McGregor et al., 1983; Chapin et al., 1985a) although effects were observed only at high doses and it is not clear whether genetic mechanisms were involved in the response.

Acute and subchronic studies have revealed that 2-methoxyethanol mainly exerts effects on the blood, kidneys, testes, spleen, central nervous system and developing fetus. Chronic studies using 2-methoxyethanol could not be located in the available literature as cited in the Appendix.

Oral and inhalation exposure to 2-methoxyethanol has resulted in fetotoxic and embryolethal effects in several species. Oral administration of 2-methoxyethanol to JCL-ICR mice at doses ranging from 31.25-1000 mg/kg/day on gestation day 7-14 resulted in fetal mortality at doses $\geq$250 mg/kg and decreased fetal weights at 125 and 250 mg/kg. The incidence of skeletal malformations was significantly higher in the 62.5, 125 and 250 mg/kg groups. Skeletal variations and retarded fetal ossification were evident in all treatment groups. Maternal effects included decreased weight gain in the $\geq$250 mg/kg groups and a decreased leukocyte count in the high-dose group. Thus, even at the lowest dose, 31.25 mg/kg, significant embryotoxic effects were observed (Nagano et al., 1981).

Phase-specific teratogenicity was elicited in CD-1 mice receiving 100-500 mg/kg 2-methoxyethanol orally during various periods between days 7 and 14 of gestation (Horton et al., 1985). Administration of 250 mg/kg/day during gestation day 7-15 resulted in gross malformations similar to those reported by Nagano et al. (1981). Exencephaly was the predominant lesion resulting from administration during the early stages of gestation (gestation days 7-9) whereas paw malformations were prevalent during later stages of development, becoming maximal on gestation day 11. Evaluation of the dose-response relationship for digit anomalies following a single dose on gestation 11 revealed a NOEL of 100 mg/kg, while malformations resulted at 175 mg/kg. At higher doses, malformations with concomitant decreases in fetal weight were observed.

The incidence of malformed fetuses (hydronephrosis, heart defects, and short limbs and tails) was significantly increased in Wistar rats receiving 159 or 319 mg/kg 2-methoxyethanol on gestation day 12. Equimolar doses of methoxyacetic acid, a metabolite of 2-methoxyethanol, were similarly potent, indicating that it may be the proximate teratogen (Ritter et al., 1985). Treatment of time-mated Sprague-Dawley rats with 25, 50 or 100 mg 2-methoxyethanol/kg/day on gestation day 7-13 resulted in a 100% resorption rate in the high-dose group and an increased incidence of gross cardiovascular malformation in the 50 mg/kg group. There was a dose-related increase in EKG abnormalities at $\geq$25 mg/kg/day, with a prolonged QRS wave being the most prevalent aberration in both the 25 and 50 mg/kg groups (Toraason et al., 1985a).

A preliminary study using monkeys indicated that oral doses of 2-methoxyethanol as low as 97 mg/kg given during short periods of pregnancy resulted either in abortions or malformed offspring (Scott, 1984).

Teratogenic responses have also been induced following inhalation exposure. Treatment of pregnant Sprague-Dawley rats on gestation days 7-13 or 14-20 or of male rats for 6 weeks with 78 mg/m^3 2-methoxyethanol, 7 hours/day resulted in significant neurochemical deviations in the brains of 21-day offspring from both maternally and paternally exposed groups (Nelson et al., 1984a). Alterations were most prevalent in the brainstem and cerebrum and less numerous in the cerebellum and midbrain. A significant decrease in avoidance conditions in offspring from dams exposed on days 7-13 was the only evidence of altered behavior. No effects on maternal or paternal animals were observed (Nelson et al., 1984a). In a related study, vapor concentrations of 2-methoxyethanol, which were not maternally toxic produced complete resorptions at 622 mg/m^3 and increased resorptions, reduced fetal weights and skeletal and cardiovascular anomalies at 311 and 156 mg/m^3 when administered 7 hours/day on gestation days 7-15 (Nelson et al., 1984b). Neither study established a no-effect level for embryotoxicity.

Hanley et al. (1984) compared the teratogenic potency of 2-methoxyethanol in CF-1 mice, F-344 rats and New Zealand White rabbits by exposing dams, 6 hours/day to 9 (rats and rabbits only), 31, or 156 mg/m^3 on gestation days 6-15 (rats and mice) and days 6-18 (rabbits). Offspring from rats and mice exposed to 156 mg/m^3 showed no evidence of a teratogenic effect, although indications of slight fetotoxicity (minor skeletal variations) were observed in both species. Exposure in the high-dose rabbit group produced significant increases in the incidence of malformations, minor variations and resorptions, as well as decreases in mean fetal body weight. Transient decreases in maternal body weight gain in all high-dose groups were the only consistent signs of maternal toxicity. No significant treatment-related effects on fetal development were observed in any species exposed to ≤ 31 mg/m^3, 6 hours/day.

Reproductive performance and testicular function can be substantially compromised by oral or inhalation exposure to 2-methoxyethanol. Treatment of rats orally with 2-methoxyethanol on gestation days 9-15 caused 100% resorptions at a 100 mg/kg/day dose level, while 50 mg/kg/day significantly depressed litter size and fetal body weights (Toraason et al., 1985b). Total resorption was also observed in CD-1 mice following oral administration of 1400 mg/kg/day 2-methoxyethanol on days 7-14 of gestation (Smith, 1983). The lowest dose of 2-methoxyethanol (estimated by the authors to be 779 mg/kg/day for males) in a 15-week drinking water study by Gulati et al. (1985) resulted in a 0 and 6% fertility index for female and male CD-1 mice, respectively. These authors additionally observed marked testicular degeneration and decreased spermatogenesis in male mice treated similarly for 19 weeks.

Reduced testicular weight and tubular degeneration were evident in F344 rats treated orally with 500 mg/kg/day 2-methoxyethanol for 4 days. No testicular changes were observed in animals given 100 mg/kg/day (Grant et al., 1985). Similar effects were reported in JCL-ICR mice given $\geq$250 mg/kg/day 2-methoxyethanol by gavage 5 times/week for 5 weeks. Animals given doses of $\leq$125 mg/kg/day exhibited no adverse effects (Nagano et al., 1979). These investigators, using the same protocol, produced testicular degeneration in Syrian golden hamsters given 62.5-500 mg/kg/day and in guinea pigs given 250 or 500 mg/kg/day (Nagano et al., 1984).

Oral ingestion of 2-methoxyethanol by Sprague-Dawley rats at dosages of 50, 100, 250 or 500 mg/kg/day for up to 11 days resulted in testicular damage characterized by primary spermatocyte lesions in all but the low-dose treatment group (Foster et al., 1983). Treatment with 500 mg/kg/day for 4 days produced widespread degeneration and decreased testis weight, effects that were reversible after 8 weeks (a period equivalent to one full maturation cycle). Similarly, F344 rats dosed orally with 100 or 200 mg/kg/day 2-methoxyethanol for 5 consecutive days exhibited time- and dose-related decreases in sperm concentration and motility as well as marked testicular degeneration. In addition, changes in testicular protein and enzyme levels were observed in these treatment groups (Chapin et al., 1985b). In both of these studies, a dose of 50 mg/kg/day did not produce significant alterations in testicular morphology or function.

Fertility was completely suppressed in male Sprague-Dawley rats exposed to 934 mg/m^3 2-methoxyethanol, 6 hours/day, 5 days/week for 13 weeks, but was partially restored at 13 weeks postexposure (Rao et al., 1983). Decreased testicular size and atrophic tubules were also observed in these animals. Female rats exposed to the same concentration did not exhibit any adverse reproductive effects. No effects on fertility and reproduction were observed at 311 mg/m^3 in rats. Doe et al. (1983), however, reported adverse reproductive effects in Wistar rats exposed to 311 mg/m^3, 6 hours/day during gestation days 6-17. Litter production and the number, weight and viability of the pups were reduced at this dose. Exposure to 934 mg/m^3 resulted in the delivery of no litters. Male rats exposed to this same dose for 10 days experienced reduced testicular weight and tubular atrophy while a dose of 311 mg/m^3 had no effect in males.

A number of effects were observed in Sprague-Dawley rats and New Zealand White rabbits exposed to 93, 311 or 934 mg/m^3 2-methoxyethanol vapor, 6 hours/day, 5 days/week for 13 weeks (Miller et al., 1983b). The high dose resulted in reduced body, thymus and testicular weights as well as hematological alterations and testicular degeneration in both species. Mortality was also increased in rabbits in the 311 and 934 mg/m^3 treatment groups.

Testicular alterations were observed in the mid- and low-dose rabbit groups, while rats at these doses displayed no apparent effects (Miller et al., 1983b). No testicular effects were found in rabbits similarly exposed to 0, 3, 10 or 30 ppm (0, 9, 31 or 93 mg/m³) for 13 weeks in another study by these investigators (Miller et al., 1982).

Following a single 4-hour exposure to 2-methoxyethanol vapor, a dose-related decrease in testis weight was observed in Alpk/AP rats 3890, 7780 or 15,560 mg/m³ 2-methoxyethanol. Minimal degenerative changes were seen in the testis of rats exposed to concentrations ≥1945 mg/m³ (Samuels et al., 1984).

A similar pattern of effects was reported by Miller et al. (1981) following exposure of F344 rats and B6C3F1 mice to 311, 934 or 3112 mg/m³ 2-methoxyethanol, 6 hours/day for a total of 9 days during an 11-day period. The high-dose groups displayed significant adverse effects on body weight gain, peripheral blood counts, bone marrow, testes and lymphoid tissues. Similar but less severe effects were observed at the 934 mg/m³ dose level.

Impaired reproductive capacity was the result of subcutaneous injection of 39 or 242 mg/kg/day 2-methoxyethanol on days 6-20 of gestation in Wistar rats. No litters were produced in the high-dose group while the low-dose animals produced fewer litters than controls (Doe, 1984).

Administration of 250 mg/kg 2-methoxyethanol by intraperitoneal injection resulted in a depleted spermatocyte population in Sprague-Dawley rats 24 hours after dosing (Moss et al., 1985).

Nonreproductive subacute and subchronic effects of 2-methoxyethanol exposure generally involve alterations in hematology, the thymus and in the central nervous system. An altered hematological profile was elicited in Wistar rats exposed to 965 mg/m³ 2-methoxyethanol, 7 hours/day, 5 days/

week for 5 weeks and in dogs similarly exposed to 2334 mg/m^3 2-methoxyethanol for 12 weeks (Werner, 1943a,b). Male F344 rats that were given 2-methoxyethanol *per os* for 4 consecutive days at doses of 100 or 500 mg/kg/day exhibited dose-dependent changes in the hematological profile that were generally reversible within 3 weeks after the cessation of treatment (Grant et al., 1985). Reversible reductions in relative kidney, spleen and thymus weights were also observed. Nagano et al. (1979) reported a sharp decrease in the white cell count of JCL-ICR mice given oral doses of 2-methoxyethanol ≥500 mg/kg/day, 5 times/week for 5 weeks. Similarly, Doe et al. (1983) reported significant reductions in a number of blood indices as well as depressed body weight gain and reduced thymus size in Wistar rats exposed to 934 mg/m^3 2-methoxyethanol, 6 hours/day for 10 consecutive days. Rats in a 311 mg/m^3 dose group were hematologically similar to controls. Alterations in biochemical parameters in isolated glial cells from Wistar rats were observed following exposure to ≥156 mg/m^3 2-methoxyethanol, 6 hours/day for up to 2 weeks (Savolainen, 1980).

Foster et al. (1983) reported that male Sprague-Dawley rats exposed to ≥100 mg/kg/day for up to 11 days experienced reductions in relative liver weight while animals given 50 mg/kg/day were unaffected. House et al. (1985) administered 2-methoxyethanol by gavage to B6C3F1 mice at dosages of 250-1000 mg/kg/day, 5 days/week for 2 weeks and noted a sharp reduction in thymus weights in the mid- and high-dose groups. Increased mortality was reported by Smith (1983) in CD-1 mice after oral administration of 1520 or 3045 mg/kg/day for 8 consecutive days. This effect was also observed following the consumption of drinking water containing 5.0% 2-methoxyethanol by CD-1 mice for 2 weeks (Gulati et al., 1985). At a drinking water concentration of 3.5%, mice suffered significant weight losses while animals maintained on water containing ≤1.0% displayed no overt effects of toxicity.

Occupational exposure to 2-methoxyethanol has generally resulted in transient hematological, neurological and renal deficits. Moderate cases of anemia and toxic encepholopathy are the signs most often reported to be the results of inhalation or dermal exposure to 2-methoxyethanol in the workplace (Donley, 1936; Parsons and Parsons, 1938; Greenburg et al., 1983; Zavon, 1963; Nitter-Hauge, 1970; Ohi and Wegman, 1978; Cohen, 1984). Occupational exposures to concentrations of ≤20 ppm (≤62 mg/m³) appear to result in no overt effects. No significant differences in hematological indices, hormone levels (follicle-stimulating hormone, luteinizing hormone and testosterone), sperm counts or numbers of abnormal sperm were observed in a group of 15 workers exposed to concentrations up to 20 ppm (Cook et al., 1982). However, given the inadequate sample sizes and minimal methodological details, the data from this study are of minimal value in establishing NOEL/LOEL levels. The TWA-TLV for 2-methoxyethanol was changed from 25 ppm (78 mg/m³) to 5 ppm (16 mg/m³) in 1984 because of the reported testicular effects in animals (ACGIH, 1986).

There are no long-term animal data on which to base an RfD for 2-methoxyethanol. Several short-term oral studies were available; however, these fail to establish a NOAEL or NOEL since Nagano et al. (1981) reported that 31.25 mg/kg/day given to mice on days 7-14 of gestation induced skeletal variations and delayed ossification in the offspring. This was the lowest dose tested in any of the oral studies. Thus, it is necessary to examine inhalation data in order to derive an RfD.

Several inhalation studies have reported a concentration of 100 ppm (311 mg/m³) administered 6-7 hours/day to a no-effect level in rats (Rao et al., 1983; Doe et al., 1983; Miller et al., 1981); however, studies by Hanley et al. (1984) and Miller et al. (1982, 1983b) are the most useful because they use several species (rats, mice and rabbits) and dose levels low enough to be noneffective. These studies suggest that the rabbit is somewhat more sensitive to the fetal and subchronic testicular effects of 2-methoxyethanol compared with rats and mice. A dose of 50 ppm (156 mg/m³), 6 hours/day during gestation that was only slightly fetotoxic in mice and rats produced a variety of malformations and variations in rabbit offspring (Hanley et al., 1984). Miller et al. (1983b) reported that 30 ppm (93 mg/m³), 6 hours/day, 5 days/week for 13 weeks, which was not toxic to rats, produced a moderate degree of testicular degeneration in rabbits. In another study, however, Miller et al. (1982) found no testicular effects in rabbits exposed to 3, 10 or 30 ppm (9, 31 or 93 mg/m³), 6 hours/day, 5 days/week for 13 weeks. Furthermore, Hanley et al. (1984) reported no treatment-related effects on fetal development in any species at $\leq$10 ppm (31 mg/m³). Therefore, the 30 ppm (93 mg/m³) exposure level, 6 hours/day, 5 days/week appears to be the threshold for testicular effects and can be considered the LOAEL for subchronic exposure. The exposure level of 10 ppm (31 mg/m³), 6 hours/day is a NOEL both for developmental effects and for testicular effects and other endpoints of subchronic exposure. The exposure can be converted to an equivalent oral dose as follows:

$$1.47\ \text{mg/kg/day} = 31\ \text{mg/m}^3 \times 6\ \text{hours}/24\ \text{hours} \times 5\ \text{days}/7\ \text{days} \times 0.5 \times 1.7\ \text{m}^3/\text{day} \div 3.2\ \text{kg}$$

where: 0.5 = absorption factor
1.7 m³/day = the daily breathing volume of a 3.2 kg rabbit (U.S. EPA, 1985)
3.2 kg = the average body weight of the rabbits exposed to 10 ppm in the study by Miller et al. (1982).

Dividing the dose of 1.47 mg/kg/day by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 to protect sensitive individuals and 10 to approximate chronic exposure) results in an RfD of 0.001 mg/kg/day or 0.1 mg/day for a 70 kg man.

An alternate approach to the RfD derivation is to use the TLV of 5 ppm (16 mg/m³), which is considered to be protective against testicular effects as well as other endpoints of toxicity (ACGIH, 1986). Before 1982, the TLV was 25 ppm (78 mg/m³), but was lowered because of the reported testicular effects in animals. An equivalent oral dose can be calculated as follows:

$$0.8 \text{ mg/kg/day} = 16 \text{ mg/m}^3 \times 5 \text{ days/7 days} \times 0.5 \times 10 \text{ m}^3\text{/day} \div 70 \text{ kg}$$

where: 0.5 = absorption factor
10 m³/day = average breathing volume in an 8-hour workday
70 kg = reference human body weight

Dividing by an uncertainty factor of 10 to protect the most sensitive individuals results in an RfD of 0.08 mg/kg/day or 5.6 mg/day for a 70 kg man.

The RfD of 0.08 mg/kg/day is 50 times greater than that derived from the animal subchronic NOEL. In addition, lack of human data in support of the TLV and uncertainties associated with the studies used in the derivation of the TLV preclude the use of the TLV for calculating an RfD. Therefore, the RfD of 0.001 mg/kg/day derived from the Miller et al. (1982) subchronic inhalation study is recommended to provide adequate protection against adverse human health effects.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The oral and inhalation toxicities for 2-methoxyethanol are summarized in Table 9-1. Most studies were conducted either during gestation or for a period of ≤ 13 weeks. The more severe effects demonstrated involved damage to the fetus and testis and impaired reproductive ability in animals and anemia and CNS effects in humans. For the animal studies, human equivalent doses were calculated by multiplying the TWA daily dosages by the cube root of the body weight ratio. The corresponding human MEDs, RV_d, RV_e, CS and RQ values for those studies judged most appropriate for the calculation of a CS and an RQ can be found in Table 9-2.

Testicular degeneration and decreased spermatogenesis have been observed in rats (Chapin et al., 1985a,b) and mice (Nagano et al., 1979) following oral administration and in rabbits (Miller et al., 1983b) following inhalation exposure. The CS values corresponding to the MEDs for these studies were very similar, ranging from 19.2-20.8. Other studies have also produced harmful effects in the testis using oral (Grant et al., 1985; Foster et al., 1983; Chapin and Lamb, 1984; Gulati et al., 1985; Nagano et al., 1984) and inhalation (Rao et al., 1983; Doe et al., 1983; Miller et al., 1983b) exposures (see Table 9-1 and Section 5.4.).

MEDs (extrapolated to chronic doses) of 42 mg/day for reduced body weights and 147 mg/day for various organ and blood anomalies in rats were calculated for the studies by Miller et al. (1981, 1983b). These correspond to CS values of 12.4 and 15.4, respectively, and an RQ of 1000.

TABLE 9-1

Toxicity Summary for 2-Methoxyethanol

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)[a]	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Oral	rat/Wistar	F	6-8	NR	undiluted	NR	0.165-0.330 mg/kg, gestational day 12	159-318	27-54	Increased incidence of embryotoxicity	Ritter et al., 1985
Oral	rat/Sprague-Dawley	F	8-11	0.30	water	NR	25-50 mg/kg/day, gestational days 7-13	25-50	4-8	Fetal cardiovascular defects	Toraason et al., 1985a
			8-11	NR			100 mg/kg/day, gestational days 7-13	100	17	100% resorptions	
Oral	rat/Wistar	F	15	NR	saline	NR	200 mg/kg (duration NR)	200	34	100% resorptions	Doe, 1984
Oral	rat/NR	F	NR	NR	water	NR	50 mg/kg, gestational days 9-15	50	9	Increased feto-toxicity	Toraason et al., 1985b
			NR	NR	water	NR	100 mg/kg, gestational days 9-15	100	17	100% resorptions	
Oral	rat/F344	M	24	0.105	water	99.9%	100 mg/kg/day for 4 days	100	11	Transient decreases in organ weights; lymphocytopenia	Grant et al., 1985
			24	0.091			500 mg/kg/day for 4 days	500	55	Thymic atrophy; lymphocytopenia; neutropenia; testicular atrophy	
Oral	rat/Sprague-Dawley	M	36	NR	water	99.9%	50 mg/kg/day for 11 days	50	9	No effects	Foster et al., 1983
Oral	rat/Sprague-Dawley	M	36	NR	water	99.9%	100 mg/kg/day for 11 days	100	17	Spermatocyte degeneration	Foster et al., 1983
			36	NR			250-500 mg/kg/day for 11 days	250-500	43-85	Decreased testes weight; spermatocyte and spermatid degeneration	

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)^a	Equivalent Human Dose (mg/kg/day)^b	Response	Reference
Oral	rat/Sprague-Dawley	M	24	NR			500 mg/kg/day for 4 days	500	85	Decreased relative liver and testes weight; decreased spermatogenesis	Foster et al., 1983
Oral	rat/F344	M	12-20	NR	water	NR	50 mg/kg/day for 5 days	50	9	No effects	Chapin et al., 1985a,b
			12-20	NR			100-200 mg/kg/day for 5 days	100-200	17-34	Decreased fertility; decreased sperm count, motility; increased sperm malformations; altered testis histology; enzyme activity	
Oral	rat/344	M	8	NR	water	NR	150 mg/kg/day for 10 days	150	26	Spermatocyte necrosis; decreased testes weight	Chapin and Lamb, 1984
Oral	mouse/CD-1	F	9-12	0.035	water	99.9%	250 mg/kg/day various intervals between gestation days 7 and 11	250	20	Increased resorptions; decreased fetal body weight	Horton et al., 1985
			9-16	0.035			500 mg/kg/day on gestation day 9, 10, 11, 12 or 13	500	40	Increased resorptions; decreased fetal body weight; digit malformations; vertebral fusion	
			10	0.035			250 mg/kg/day, gestation days 7-14, 7-9, 8-10 or 9-11	250	20	Exencephaly; digit malformations; vertebral fusion	
Oral	mouse/CD-1	F	11	0.04	water	>99.9%	100 mg/kg/day on gestation day 11	100	8	No effects	Horton et al., 1985
			10	0.039			175 mg/kg/day on gestation day 11	175	14	Digit anomalies	

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)^a	Equivalent Human Dose (mg/kg/day)^b	Response	Reference
Oral	mouse/CD-1	F	9-11	0.037			250-450 mg/kg/day on gestation day day 11	250-450	20-36	Digit anomalies; reduced fetal body weight	Horton et al., 1985
Oral	mouse/JCL-ICR	F	21	0.040	water	NR	31.25 mg/kg/day on gestation days 7-14	31.25	3	Skeletal variations; delayed ossification	Nagano et al., 1981
			24	0.040			62.5 mg/kg/day on gestation days 7-15	62.5	5	Same as above; skeletal malformations	
			24	0.040			125 mg/kg/day on gestation days 7-15	125	10	Same as above; reduced fetal body weight	
			23-24	0.035			250-1000 mg/kg/day on gestation days 7-14	250-1000	20-79	Same as above; reduced maternal body weight gain; decreased leukocyte count (1000 mg/kg only); decreased live fetus/litter; gross anomalies	
Oral	mouse/CD-1	F	10	0.027	liquid	NR	190-760 mg/kg/day for 8 days	190-760	14-55	No effects	Smith, 1983
			10	0.025			1520-3045 mg/kg/day for 8 days	1520-3045	108-216	Increased mortality	
			50	0.028			1400 mg/kg/day on gestation days 7-14	1400	103	Total resorption of all litters; increased maternal mortality	
Oral	mouse/CD-1	M	8	0.035	drinking water	NR	0.25-1.0% for 14 days	420-1090^c	33-87	No effects	Gulati et al., 1985
		F	8	0.027				520-1750^c	38-127	No effects	

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)^a	Equivalent Human Dose (mg/kg/day)^b	Response	Reference
Oral	mouse/CD-1	M	8	0.031			2.5% for 14 days	2340^c	178	Decreased body weight gain; increased mortality	Gulati et al., 1985
		F	8	0.024				2860^c	200	Decreased body weight	
		M	8	0.028			5.0% for 14 days	2480^c	183	Decreased body weight increased mortality	
		F	8	0.021				2620^c	175	Same as above	
		M	20	0.034			0.5% for 15 weeks	779^c	61	Decreased fertility; increased mortality; testicular atrophy; altered sperm parameters	
		F	20	0.027				1032^d	75	Decreased fertility; increased mortality	
		M	20	0.031			1.0-2.0% for for 15 weeks	$1270\text{-}1909^c$	97-146	Same as above	
		F	20	0.024-0.022				$1845\text{-}2993^d$	129-203	Same as above	
Oral	mouse/JCL-ICR	M	5	NR	water	NR	62.5-125 mg/kg/day, 5 days/week, 5 weeks	45-89	3-7	No effects	Nagano et al., 1979
			5	NR			250 mg/kg/day, 5 days/week, 5 weeks	179	13	Depressed spermatogenesis	
Oral	mouse/JCL-ICR	M	5	NR	water	NR	500-2000 mg/kg/day, 5 days/week, 5 weeks	357-1429	27-108	Decreased testes weight; testicular atrophy; depressed spermatogenesis; decreased white blood cell count (≥1000 mg/kg); decreased hemoglobin (2000 mg/kg only)	Nagano et al., 1979

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)[a]	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Oral	mouse/JCL-ICR	M	8	0.026	drinking water	NR	2.5% for 18 days	4808[e]	346	Decreased body and testis weight; decreased mean white blood cell count	Nagano et al., 1979
Oral	mouse/B6C3F1	F	10	0.022	water	NR	250 mg/kg/day, 5 days/week, 2 weeks	179	12	No effect	[illegible] et al., 1985
				0.021			500-1000 mg/kg/day, 5 days/week, 2 weeks	357-714	24-48	Depressed thymus weight	
Oral	hamster/ Syrian	M	4	0.122	water	NR	62.5-500 mg/kg/day, 5 days/week, 5 weeks	45-357	5-43	Decreased testes weight	Nagano et al., 1984
	guinea pigs/ Syrian	M	3	0.769			250-500 mg/kg/day, 5 days/week, 5 weeks	179-357	40-79	Decreased testes weight; depressed white blood cell count	
Inhalation	rat/Sprague-Dawley	M	18	0.355	vapor	≥98%	25 ppm (78 mg/m³), 7 hours/day, 7 days/week for 6 weeks	14	2	Neurochemical deviations in 21-day-old offspring	Nelson et al., 1984a
		F	16	NR			25 ppm (78 mg/m³), 7 hours/day, gestation days 7-13 or 14-20	14	2	Same as above; slight behavioral effects (gestation days 7-13)	
Inhalation	rat/Sprague-Dawley	F	14-34	0.30	vapor	98-99.5%	50-100 ppm (156-311 mg/m³),7 hours/day, gestation days 7-15	30-61	5-10	Increased resorptions; decreased fetal weight; visceral and skeletal malformations	Nelson et al., 1984b

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)[a]	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Inhalation	rat/Sprague-Dawley	F	8	0.30			200 ppm (622-mg/m³), 7 hours/day, gestation days 7-15	122	20	100% resorptions	Nelson et al., 1984b
Inhalation	rat/F-344	F	31	0.20	vapor	99.96%	10 ppm (31 mg/m³), 6 hours/day, gestation days 6-15	6	0.9	No effects	Hanley et al., 1984
			30	0.20			50 ppm (156 mg/m³), 6 hours/day gestation days 6-15	30	4	Slight fetoxocity	
Inhalation	rat/Sprague-Dawley	F	20	0.28	vapor	≥99.7%	100 ppm (311 mg/m³), 6 hours/day, 5 days/week, 13 weeks	38	6	No effects	Rao et al., 1983
			20	0.26			200 ppm (622 mg/m³), 6 hours/day, 5 days/week, 13 weeks	78	12	Decreased body weight	
Inhalation	rat/Sprague-Dawley	M	20	0.475	vapor	≥99.7%	100 ppm (311 mg/m³), 6 hours/day, 5 days/week, 13 weeks	32	6	No effects	Rao et al., 1983
			20	0.425			300 ppm (934 mg/m³), 6 hours/day, 5 days/week, 13 weeks	99	18	Decreased body weight; completely suppressed fertility (partially reversible); testicular degeneration	

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)[a]	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Inhalation	rat/Wistar	F	20	NR	vapor	99%	100 ppm (311 mg/m^3), 6 hours/day, gestation days 6-17	49	8	Decreased number of litters produced; reduced number, weight, viability of pups	Doe et al., 1983
			20	NR			300 ppm (934 mg/m^3), 6 hours/day, gestation days 6-17	149	25	Reduced maternal body weight; no litters produced	
Inhalation	rat/Wistar	M	10	NR	vapor	99%	100 ppm (311 mg/m^3), 6 hours/day, 10 days	50	9	No effects	Doe et al., 1983
			10	NR			300 ppm (934 mg/m^3), 6 hours/day, 10 days	149	25	Reduced body weight; reduced testicular weight; testicular atrophy; altered hematology	
Inhalation	rat/Sprague-Dawley	M	10	0.44	vapor	≥99.7%	100 ppm (311 mg/m^3), 6 hours/day, 5 days/week, 13 weeks	33	6	No effects	Miller et al., 1983b
			10	0.40			300 ppm (934 mg/m^3), 6 hours/day, 5 days/week, 13 weeks	101	18	Reduced body weight; reduced thymus weight; altered hematology; testicular and thymic atrophy	
Inhalation	rat/Sprague-Dawley	F	10	0.255	vapor	≥99.7%	30 ppm (93 mg/m^3), 6 hours/day, 5 days/week, 13 weeks	12	2	No effects	Miller et al., 1983b
			10	0.245			100 ppm (311 mg/m^3), 6 hours/day, 5 days/week, 13 weeks	40	6	Reduced body weight	

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)[a]	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Inhalation	rat/Sprague-Dawley	F	10	0.235			300 ppm (934 mg/m^3), 6 hours/day, 5 days/week, 13 weeks	121	18	Reduced body weight; reduced thymus weight; altered hematology; thymic atrophy	Miller et al., 1983b
Inhalation	rat/F-344	M/F	5/5	0.22/ 0.13	vapor	>99%	100 ppm (311 mg/m^3), 6 hours/day 9 days over an 11-day period	47/56	7/7	No effects	Miller et al., 1981
		M/F	5/5	0.22/ 0.13			300 ppm (934 mg/m^3), 6 hours/day 9 days over an 11-day period	142/169	21/21	Reduced thymus weight; altered hematology; bone marrow, testes and lymphoid tissue histopathology	
		M/F	5	0.20/ 0.12			1000 ppm (3112 mg/m^3), 6 hours/day 9 days over an 11-day period	490/578	69/69	Same as above reduced body weight; reduced testes weight	
Inhalation	rat/Wistar	M/F	23	0.21	vapor	NR	310 ppm (965 mg/m^3), 7 hours/day, 5 days/week, 5 weeks	152	22	Hemosiderosis-M spleen; bone marrow changes; altered hematology	Werner et al., 1943a
Inhalation	mouse/CF-1	F	30	0.04	vapor	99.96%	10 ppm (31 mg/m^3), 6 hours/day, gestation days 6-15	9	0-7	No effects	Hanley et al., 1984
			32	0.04			50 ppm (156 mg/m^3), 6 hours/day, gestation days 6-15	46	4	Decreased body weight gain; slight fetotoxicity	

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)[a]	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Inhalation	mouse/B6C3F1	M/F	5/5	0.028/ 0.022	vapor	>99%	300 ppm (934 mg/m^3), 6 hours/day for 9 days over 11-day period	309/340	23/23	No effects	Hanley et al., 1984
			5/5	0.028/ 0.022			1000 ppm (3112 mg/m^3), 6 hours/day for 9 days over an 11-day period	1028/1132	76/77	Reduced thymus and testes weight; altered hematology	
Inhalation	rabbit/New Zealand White	M/F	5/5	4.3/4.8	vapor	≥99.6%	30 ppm (93 mg/m^3), 6 hours/day, 5 days/week, 13 weeks	9/9	4/4	Decreased testes size; degenerative changes in testes of one male	Miller et al., 1983b
			5/5	4.8/3.8			100 ppm (311 mg/m^3), 6 hours/day, 5 days/week, 13 weeks	28/29	11/11	Increased mortality; decreased testes size, decreased lymphoid tissue (females); lymphoid and testicular atrophy	
			5/5	3.7/3.9			300 ppm (934 mg/m^3), 6 hours/day, 5 days/week, 13 weeks	87/87	33/33	Same as above; decreased thymus and testes weight; altered hematology	
Inhalation	rabbit/New Zealand White	M	29	4.0	vapor	99.96%	10 ppm (31 mg/m^3), 6 hours/day, gestation days 6-18	4	2	No effects	Hanley et al., 1984
Inhalation	rabbit/New Zealand White	M	30	4.2	vapor	99.96%	50 ppm (156 mg/m^3), 6 hours/day, gestation days 6-18	20	8	Decreased maternal body weight gain; increased resorptions; decreased fetal body weight; increased external and soft tissue malformations and variations	Hanley et al., 1984

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)[a]	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Occupational	human	M	19	70	vapor	NR	25 ppm (78 mg/m^3), occupational	NA	8[f]	Anemia, fatigue, abnormal reflexes and tremors	Greenburg et al., 1938

[a] For inhalation studies, doses were determined by multiplying the vapor concentrations (in mg/m^3) by the daily animal breathing rate calculated for rats and mice according to U.S. EPA (1980) and for rabbits according to U.S. EPA (1985). The dose is expressed as a TWA and is divided by the reported or default animal weight.

[b] Calculated by multiplying the transformed animal dose by the cube root of the animal to human body weight ratio. When animal weight was not provided, the following default values were used: mouse, 0.03 kg; rat, 0.35 kg.

[c] Calculated by authors

[d] Estimated from body weight and water consumption data

[e] Assuming water consumption of 5 ml/day (U.S. EPA, 1985); this value may be high since water consumption data from Gulati et al. (1985) indicate lower daily intakes in mice given water containing 2.5% 2-methoxyethanol.

[f] Calculated by multiplying the occupational exposure level by 5/7 days and by 10 m^3/day and dividing by 70 kg.

NR = Not reported; NA = not applicable

TABLE 9-2

Composite Scores for 2-Methoxyethanol

Compound	Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	rat/F-344	100	119[a]	2.4	Decreased fertility; testicular lesions; altered sperm parameters	8	19.2	1000	Chapin et al., 1985a,b
Oral	mouse/ JCL-ICR	179	91[a]	2.6	Depressed spermatogenesis	8	20.8	1000	Nagano et al., 1979
Inhalation	rabbit/ New Zealand	9	28[a]	3.3	Testicular degeneration	6	19.8	1000	Miller et al., 1983b
Inhalation	rat/Sprague-Dawley	40	42[a]	3.1	Reduced body weight	4	12.4	1000	Miller et al., 1983b
	rat/F-344	169	147[a]	2.2	Organ weight changes altered hematology; various tissue lesions	7	15.4	1000	Miller et al., 1981
Inhalation	rat/Sprague-Dawley	14	14[a]	3.8	Neurochemical deviations in offspring without behavioral alterations	7	26.6	100	Nelson et al., 1984a
Oral	mouse/ JCL-ICR	31.25	210	2.0	Fetotoxicity without maternal toxicity	8	16	1000	Nagano et al., 1981
Oral	mouse/CD-1	175	98[a,b]	2.5	Digit anomalies	10	25	100	Horton et al., 1985
Occupational	human	NA	500	2	Anemia, CNS toxicity	7	14	1000	Greenburg et al., 1938

[a] Uncertainty factor of 10 was incorporated to extrapolate a chronic human MED.

[b] Dose was given only on gestation day 11 and is therefore considered subchronic to the life of the fetus.

The majority of the 2-methoxyethanol toxicity literature consists of pre-mating and gestational-exposure studies. Reproductive impairment, fetotoxicity and teratogenicity have been reported following oral and inhalation exposures in males and females. A CS of 26.6 was calculated from the data of Nelson et al. (1984a) who reported significant neurochemical alterations in the brains of 21-day-old offspring produced from untreated females and males treated 7 hours/day for 6 weeks with 25 ppm (78 mg/m^3) 2-methoxyethanol. This dose corresponds to a chronic human MED of 14 mg/day and an RQ of 100. Nagano et al. (1981) reported that a dose of 31.25 mg/kg/day resulted in fetotoxicity in mice; the dose corresponds to a chronic human MED of 210 mg/day, a CS of 16 and an RQ of 1000. Horton et al. (1985) determined that a dose of 175 mg/kg/day was sufficient to induce digit malformations in mice, thus allowing the derivation of a CS value of 25. Other studies have produced damaging effects in the fetus using oral (Ritter et al., 1985; Toraason et al., 1985a,b; Doe, 1984, Smith, 1983) and inhalation (Hanley et al., 1984; Doe et al., 1983) exposure (see Table 9-1 and Sections 5.3. and 5.4.).

The MED for anemia and CNS toxicity in humans occupationally exposed to $\geq$25 ppm (>78 mg/m^3) (Greenburg et al., 1938) is 560 mg/day, which corresponded to an RV_d of 2. The effects warrant an RV_e of 7 with a resultant CS of 14 corresponding to an RQ of 1000.

Although chronic studies are not available, Table 9-1 demonstrates that the subchronic data are adequate for deriving CS values for a number of effects. There is notable consistency among the CS values for each type of effect. The literature strongly suggests that the fetus and testis are most at risk from 2-methoxyethanol either from oral or inhalation exposure, and this is reflected in the generally higher CS values for those effects. The data of Nelson et al. (1984a), resulting in the highest CS of 26.6, is recommended in establishing a proposed RQ (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

There are no data available concerning the carcinogenicity of 2-methoxyethanol. According to the hazard ranking scheme for carcinogenicity for RQs under CERCLA, 2-methoxyethanol is a CAG Group D compound (U.S. EPA, 1986c), which indicates that no direct ranking is possible because of the lack of data.

TABLE 9-3

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose*:	14 mg/day
Effect:	neurochemical deviations in offspring
Reference:	Nelson et al., 1984a
RV_d:	3.8
RV_e:	7
Composite Score:	26.6
RQ:	100

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*Equivalent human dose

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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